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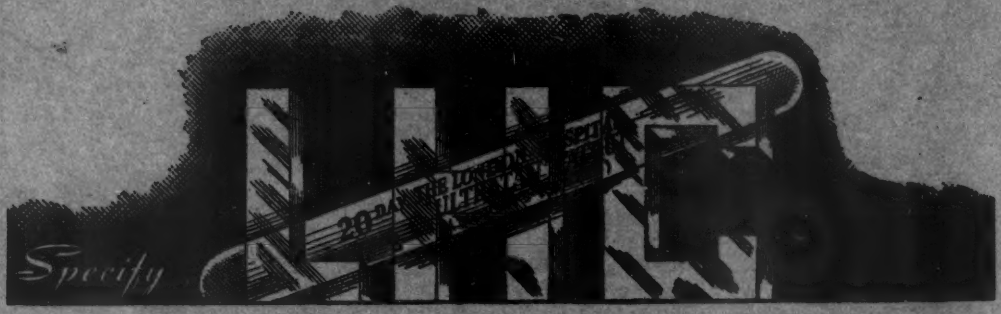

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The Journal of
Obstetrics & Gynaecology
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Persistent Functional Corpus Luteum

BY

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A PERSISTENT corpus luteum is loosely regarded in clinical gynæcology as being a possible cause of amenorrhoea. It is reasonable to suppose from what is known of pregnancy that a persistent corpus luteum, if it occurs, might give rise to amenorrhoea, producing in fact a condition which may be regarded as a pseudo-pregnancy. Unfortunately, in the available literature, there is scanty histological evidence to substantiate this clinical presumption.

Fluhmann[1] states: "The ovary may take an active part in the production of an amenorrhoea of short duration, when a corpus luteum fails to undergo degeneration and persists as a functioning structure. In such cases the endometrium is in a stage of secretion and there are signs of pseudo-pregnancy. Although a number of such cases have been described in recent years, they are probably unusual. In long cycles of 35 to 45 days it is believed that the post-ovulatory phase may be unduly prolonged, and it is difficult to accept such instances as representing a period of amenorrhoea. Some years ago Novak and Te Linde also pointed to the difficulty of establishing a diagnosis of amenorrhoea due to corpus luteum persistence in view of the possibility that such cases may be attributed to an unrecognized ectopic gestation."

While there is some literature concerning the relation of cysts

of the corpus luteum in amenorrhoea (Ehrhardt and Kramann[2]) there is, unfortunately, no evidence available to show that a non-cystic, apparently normal, corpus luteum can produce amenorrhoea for as long as 18 weeks.

Biological tests are still not available for assessing accurately the activity of the corpus luteum in the human female. Furthermore, it has not been possible with available criteria to assess readily by histological means the functional activity of a corpus luteum. Apart from the fluctuations of the colloid droplets described by Rabl,[3] and later by Pinto,[4] Seitz,[5] Miller,[6] Marcotty,[7] and Portes, Aschheim and Robey;[8] and of the lipoid described by Marcotty and by Moulonguet-Doleris,[9] there are no satisfactory criteria to assist in reliably distinguishing between the corpus luteum of menstruation and pregnancy. In fact, it is generally regarded that the pregnancy corpus luteum is merely an intensification of the menstrual corpus luteum.

A case clinically diagnosed as endometriosis, and associated with amenorrhoea of 18 weeks' duration, was found at operation to exhibit only a large corpus luteum, with no other evidence of gross ovarian pathology. Macroscopic examination seemed to suggest that we were dealing with a persistent corpus luteum. Our preliminary studies of the corpus luteum revealed that it had close affinities with the corpora lutea of the first half of pregnancy using the criteria of Gillman and Stein[10] and based on proven cases of intra-uterine pregnancy.

The object of the present paper is, firstly, to describe the histological appearance of this unusual corpus luteum, the fragment of ovary and the endometrium; secondly, to examine critically the criteria suggested by Gillman and Stein for the corpus luteum of pregnancy; thirdly, to assess the medico-legal value of colloid as a diagnostic feature of the corpus luteum of pregnancy; fourthly, to draw attention to the small yellow bodies in the ovary; fifthly, to determine whether the so-called balloon cells of Sturgis[11] are diagnostic of pregnancy; sixthly, to ascertain the value of basal fat in the uterine gland cells as an indication of progesterone activity; and finally, to examine the nature of the decidual reaction in the endometrium associated with this persistent corpus luteum.

Case History

A.M.L., aged 29 years, was admitted to the Johannesburg General Hospital on October 20th, 1940 (hospital index number 11044), complaining of pain in the right hypogastrium for 3 to 4 years; amenorrhoea for 4 months.

Menstruation. Age 14. 7/25 to 35. Normal loss. Last menstrual period June 17th, 1940. Bled for one day on September 24th, 1940, the blood being dark and offensive. Dysmenorrhoea present; the pain starts one day before the period and lasts for 3 days. Previously it was present for only one day, but recently the severity and duration of the pain have increased.

Pregnancies. None.

Leucorrhoea. Slight, yellowish, irritating at times. Increased since marriage, 6 months.

Micturition. Slight frequency and urgency. Burning on micturition for about 3 years.

Defaecation. Rather constipated. The pain is increased when constipated.

Weight. Decrease from 110 to 100 pounds in last 6 months.

Illnesses and operations. Appendicectomy 1929. Tonsils and adenoids removed 5 to 6 years ago. Inflammation of breast at 14 years.

After the operation in 1929 the patient was free of pain until 3 to 4 years ago when she developed pain in the right hypogastrium. At first there were attacks of severe, sharp pain lasting about half an hour occurring every 6 months. The frequency of the attacks has gradually increased, and now a continuous, dull ache with almost daily attacks of acute sharp pain, aggravated by movement, standing and defaecation. Dyspareunia present; the pain is felt in the right hypogastrium and comes on immediately after the act, lasting for a few hours.

The patient has never missed a period until this year, her last period being June 17th, 1940. On September 24th, 1940, she bled for one day. She states that there is frigidity. She is anxious to have children.

During the last 2 months she has noticed enlargement of the breasts, and tenderness of the left mamma particularly. This normally occurs before menstruation but has been present now for 2 months.

Examination. General examination did not reveal anything abnormal.

Abdomen. Midline subumbilical scar. Tender over lower abdomen particularly in right hypogastrium and iliac fossa.

Vaginal. Vulva: labia small. Vagina: tenderness deep to introitus. Walls well supported. Cervix: long, large, firm; os small. Tenderness on movement, especially lateral movement. Cervix points backwards and is situated rather low. Uterus: anteverted, small, mobile. Normal consistence, regular, not pregnant. Appendages: *Right* very tender. Firm, rounded mass about 1½ inches in diameter, apparently fixed to right side of uterus. *Left* tender. Mass not felt. There was also tenderness in the posterior fornix. Discharge: white, watery, moderate amount.

Diagnosis. Ovarian endometriosis.

The Friedman pregnancy test was not made.

In view of the symptoms and on account of the tentative diagnosis of endometriosis, it was decided to perform a laparotomy.

Operation, October 22nd, 1940.

Curettage was first performed. The endometrium was hypertrophied, but otherwise appeared normal. The abdominal scar was then excised and the abdomen opened. The right ovary was the seat of a large corpus luteum. The uterus was small even for a nullipara and normal to the naked eye. The left ovary was small, slightly crenated, and appeared perfectly normal; a corpus luteum was not present.

The yellowish body on the right ovary was resected with some of the surrounding tissue which was seen to contain a few small yellow masses.

There were a few light adhesions around both Fallopian tubes, and these were broken down without causing haemorrhage or damage to surrounding structures. Retrograde insufflation was carried out; air did not pass through the left tube, but on the right side air did pass. There was no evidence of ectopic pregnancy. The large corpus luteum associated with the smaller yellow bodies excited some curiosity about the exact nature of these findings in the ovary.

On the 2nd day of the operation, there was scanty haemorrhage *per vaginam,* which lasted one day. Convalescence was uneventful, and the patient was discharged on the 14th day. When the patient reported again, she stated that she had had a menstrual period on Nov. 20th, 1940, *i.e.* 29 days after the operation or 27 days after the post-operative bleeding. The loss lasted for 2 days, but was profuse, and clots were present. Whereas previously 3 pads per day were required, on this occasion 24 pads were used.

The patient was seen once again, and this time she complained that, on the 14th day of the cycle, she had severe pain in the right side of the pelvis lasting for about 2 days.

At the operation the bulging mass on the right ovary was removed with the surrounding ovarian tissue. The rest of the ovary was left. The other ovary was macroscopically normal. On section the mass on the ovary proved to be a corpus luteum with the following dimensions: $15 \times 15 \times 10$ mm. Lutein tissue varied from 2 mm. to 5 mm. in width in section. The corpus luteum was pale yellow in colour, and the lutein tissue formed a thick rim around a central core of connective tissue which only in part showed the presence of macroscopically visible blood. Deep to the fibrous band, and occupying the centre part of the corpus luteum, was a small coagulum 7×2 mm. in size, which on sec-

tion represented 10 per cent of the area of the whole corpus luteum.

In the fragment of ovarian tissue surrounding the corpus luteum there were half-a-dozen small bodies measuring 3 to 4 mm. Some of these were solid, haemorrhagic bodies, and others consisted of small follicles surrounded by a rim of orange-yellow tissue.

Histology of the Corpus Luteum

Under the low power of the microscope (Fig. 1) the corpus luteum is seen to possess an external false capsule (*ec*) continuous with the ovarian stroma. This capsule is much denser than the surrounding ovarian stroma. In this false capsule lie the blood-vessels and lymphatics. The blood-vessels form a prominent feature, and their walls are very much thickened. These blood-vessels are applied to the underlying layer of thecal interna cells.

The false capsule sends down robust trabeculae into the substance of the glandular tissue and divides it into irregular-sized lobules. Some of these trabeculae establish contact with trabeculae which pass out from the layer of connective tissue separating the glandular part from the central core of connective tissue. The majority of the trabeculae coming from the external capsule on the one hand, and those passing outward from the inner band of connective tissue (*fb*) on the other hand, interdigitate and give the lutein tissue a folded appearance. Passing out from these two types of septa are fine reticular fibres which form the scaffolding for the gland cells and the blood capillaries.

The glandular tissue of the corpus luteum consists largely of granulosa lutein cells and to a lesser extent of the theca lutein cells. The theca lutein cells almost form a complete capsule to the granulosa lutein cells, being very thick in some places and thinner in others. They are arranged in clusters simulating alveoli, and they pass down into the substance of the corpus luteum along the trabeculae where they may form a sheath to the blood-vessels. On account of the way in which the corpus luteum was enucleated, the ratio of theca to granulosa lutein cells could not be precisely determined. The theca lutein cells certainly reached a degree of development, much greater than is usually encountered in the corpus luteum of menstruation, and equal if not greater than that of the corpus luteum of pregnancy, when these cells are at their maximum degree of development. In one region where the theca interna is particularly highly

developed there is a marked dilatation and even a rupture of the capillaries.

Theca Lutein Cells

Under the high power the theca lutein cells (Fig. 2) are of two types, with all transitional forms between them.

The first type comprises a cell which, with haematoxylin and eosin staining, shows fairly regular and sharply defined walls. The maximum diameter is 15 to 20 μ. The cytoplasm is finely granular and shows an affinity for eosin, and contains very few vacuoles. The nucleus tends to be centrally situated within the cell. The nuclei are relatively small; many are hyperchromatic and they contain 2 irregularly shaped nucleoli. Some of the nuclei may be so pyknotic that it is impossible to distinguish their architecture. These cells with eosinophilic cytoplasm occur in clusters and are very much less numerous than the second type or clear cell.

The second type of cell is far more numerous than the dark cell. The size varies within wide limits. In some cases it is so large that it can easily be mistaken for one of the granulosa lutein cells; in other cases, although small, it is still a little larger than the first type, or dark cell. The cell walls are very ill-defined when the cytoplasm is clear and highly vacuolated. These cells when arranged in clusters resemble very closely the cells lying in the zona glomerulosa of the suprarenal gland. The cytoplasm of these clear cells may be finely granular with a slight affinity for eosin, or the cytoplasm may consist of a very large number of small, discrete vacuoles. These vacuoles fuse, and in some cases there may be three to six large vacuoles separated by very delicate strands of cytoplasm which merge with a non-vacuolated, finely granular cytoplasm immediately surrounding the nucleus. In some cases even this perinuclear mass of cytoplasm may become so much reduced that it forms only a very delicate rim around the nucleus. The size and character of the nucleus vary considerably. In some, the nucleus may be large, vesicular, and contains up to four pale-staining nucleoli; in others the nucleus may be small and hyperchromatic, and it is difficult to see its detailed structure.

With Mallory's triple stain only a few cells (2.3 per cent) contain secretory granules. The granules are particularly concentrated in the dark cells. A few of the clear cells contain granules, and where they do, these granules are dispersed widely throughout the cytoplasm.

The amount of vacuolation seen in both haematoxylin and eosin and Mallory preparations is out of proportion to the amount of fat seen in the frozen section. While 59 per cent of the cells contain some fat, the amount of fat in each cell is subject to a great deal of fluctuation. In the majority of cells there may be only one or two small droplets of lipoid, and only a few cells contain many large droplets.

Granulosa Lutein Cells

The granulosa lutein cells form the bulk of the glandular tissue in the corpus luteum.

The cytoplasm of by far the larger proportion of these cells show a varying affinity for the eosin. On the basis of this reaction the granulosa lutein cells like the theca lutein can be divided into clear and dark cells; the majority of these cells are pale staining. The clear cells are spheroidal, and the dark cells are angular and flat. The nucleus of the granulosa lutein cell is one and one-half times to twice as large as that of the theca lutein cell. In the majority of the pale cells the nucleus is vesicular and contains one or more oval, round or rod-shaped nucleoli. In the dark cells the nuclei are much more hyperchromatic, and in some cases are even pyknotic. Occasional nucleoli are extruded from the nucleus into the general cytoplasm.

Cytoplasmic Inclusions.

Secretory granules. These are well demonstrated by Mallory's connective tissue stain where they appear as red or orange-red against the background of pale blue cytoplasm (Fig. 3, *g*). The granules occur in 47 per cent of granulosa lutein cells. The granules may be small and punctate, or else they may form short rods. They may be few in number or else they may crowd the whole of the cell. When they are scanty they tend to be distributed around the periphery of the cell. Occasionally a cluster of these granules may be found lying near one extremity of the cell. The granules may be found in the dark cells as well as in the pale cells and in cells which contain a few small vacuoles. In the highly vacuolated cells, especially where the whole of the cell almost consists of one large vacuole, the granules are extremely scanty and most frequently absent.

Fat.

Under low power (×80) there are from 8 to 12 cells containing large masses of lipoid in one field. Under ×400 there are

2 to 3 cells per field that contain large droplets of lipoid (Fig. 4, *gl*). Ninety per cent of the granulosa lutein cells contain some fat. There is an extensive variation in the size of the fat globules. In some cells the granules are so fine (*gs*) that they are just visible under the highest powers of the microscope (×900), while in others the globules may reach a size of 3 μ in diameter, *i.e.* almost half the size of the nucleus (Fig. 4). The fat is distributed widely throughout the cell. In some of the pale cells some of the fat has disappeared almost completely. In the cells which contain vacuoles the fat is almost absent.

In the cells which contain large droplets of fat the nucleus tends to be smaller and hyperchromatic. The larger droplets are formed by confluence of the smaller.

Nature of Fat.

With the exception of a few scattered cells the fat is isotropic. In the exceptional cells which are usually large and contain masses of granules of fat (Fig. 5), with crossed Nicol's prisms they are anisotropic (Fig. 6) and show up white in the photograph. Such collections of fat usually give a Schultz positive reaction for cholesterol.

Colloid (Fig. 7).

The true colloid only appears in occasional cells (2 per cent). There are peculiar bodies appearing in 9 per cent of cells which consist of granular bodies round or oval in shape and measuring up to 3 μ in diameter. They stain blue with Mallory's but transitional forms to colloid are present. It is for this reason that we have provisionally named these bodies "precolloid." The colloid also lies in vacuoles. The true colloid may stain blue or orange-red to yellow.

Vacuoles.

The vacuoles form a very characteristic feature of this corpus luteum (Fig. 8) and while they are scattered throughout the whole of the substance of the granulosa lutein cells, they are particularly abundant in the deepest part of the glandular tissue as it abuts against the inner fibrous core. The large number of vacuoles in the glandular tissue imparts a moth-eaten appearance to the corpus luteum. The vacuoles appear first as small, non-staining circular areas, usually located in the peripheral part of the cell (Figs. 3, *v*, 7, *v*). Then they fuse and form large vacuoles until the whole cell may consist of one vacuole which compresses

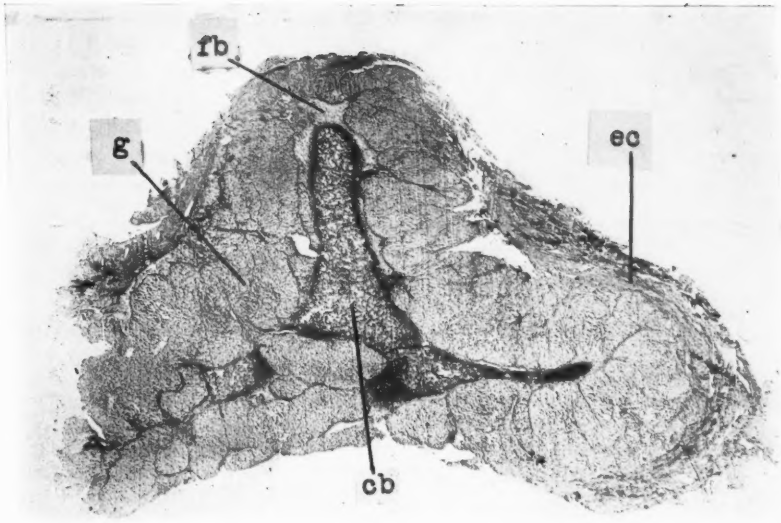

FIG. 1

Corpus luteum showing topographical arrangement of structures × 5.
cb, central coagulum; *ec*, external false capsule; *fb*, fibrous band separating lutein cells from central coagulum; *g*, granulosa lutein cells.

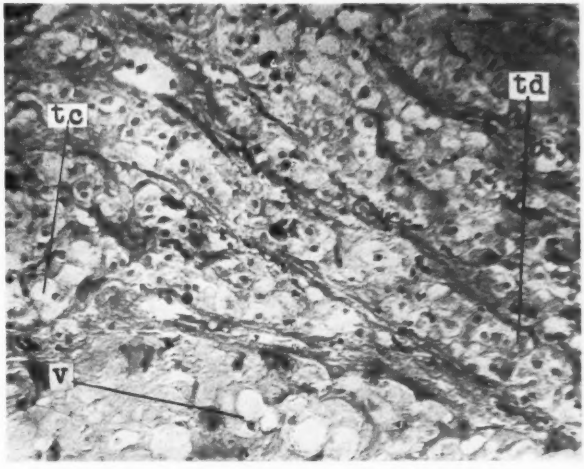

FIG. 2

Theca lutein cells × 160

tc, vacuolated thecal cells; *td*, dark thecal cells; *v*, vacuolated granulosa lutein cells.

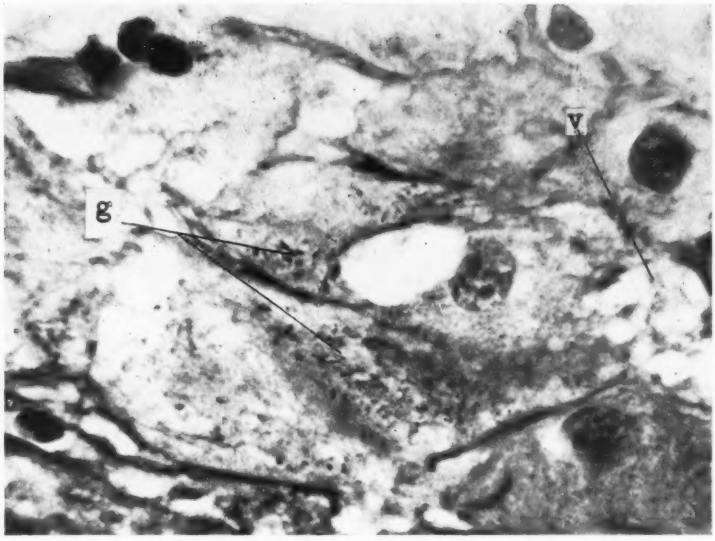

FIG. 3

Granules and vacuoles in granulosa lutein cells stained with Mallory's mixture × 1200

g, granules in granulosa lutein cells; *v*, vacuolated granulosa cells.

BL.

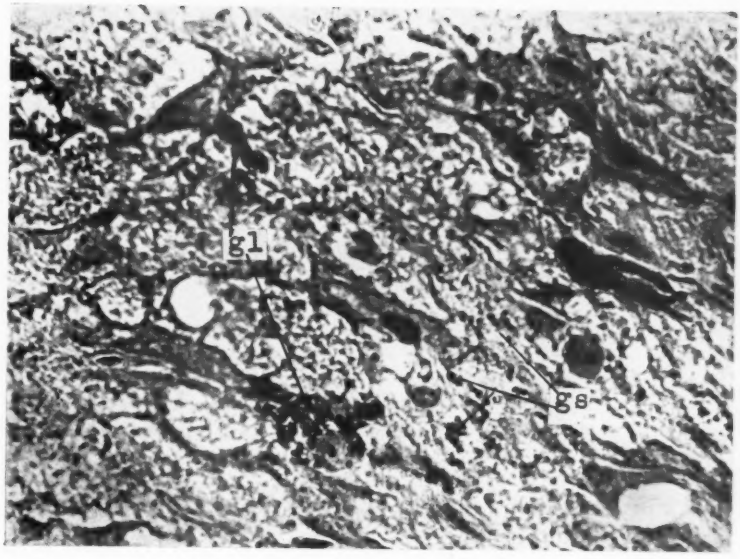

FIG. 4

Fat in granulosa lutein cells stained with Sharlach R. × 250
gl, large droplets of fat; *gs*, small globules of fat.

BL.

FIG. 5.
Fat in granulosa lutein cells.
Sharlach R. × 150.
Uncrossed Nicol's prisms.

FIG. 6.
Same as Fig. 5, but Nicol's prisms crossed. × 150.
Note the anisotropic fat showing as brilliant white. Compare this with Fig. 5.

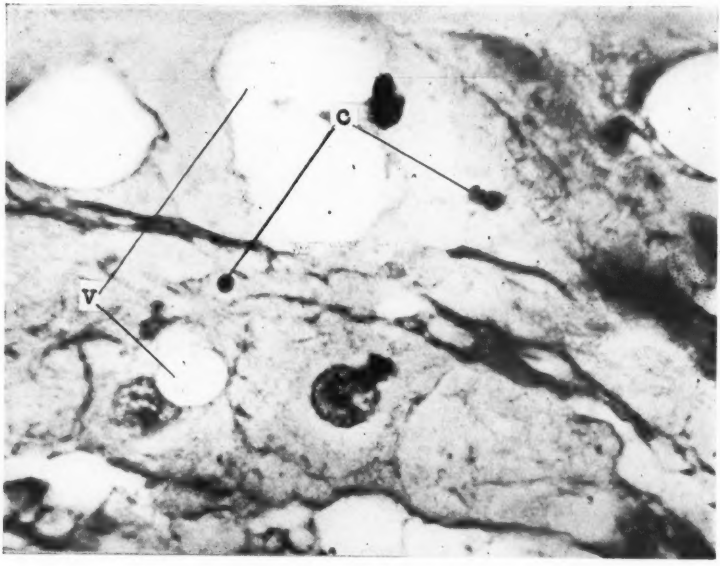

FIG. 7
Granulosa lutein cells containing droplets of colloid (*c*) and vacuolated cells (*v*). Note large vacuoles in some cells. × 1200.

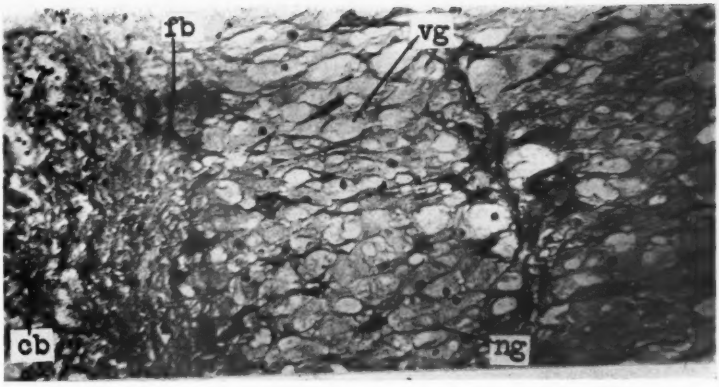

FIG. 8

Inner margin of corpus luteum × 75

cb, central coagulum; *fb*, fibrous band separating lutein cells from central coagulum; *ng*, non-vacuolated granulosa lutein cells; *vg*, vacuolated granulosa lutein cells.

BL.

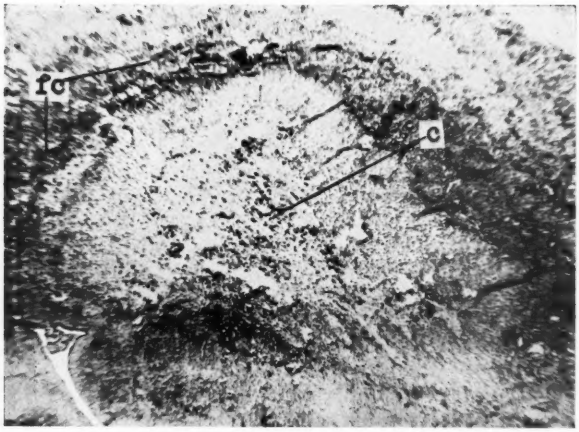

FIG. 9

Small yellow body × 25
fc, false capsule; *c*, central oedematous core with masses of pigment containing histiocytes.

FIG. 10

Small yellow body, same as Fig. 9, showing lipoid containing cells stained with Sharlach R. × 200

BL.

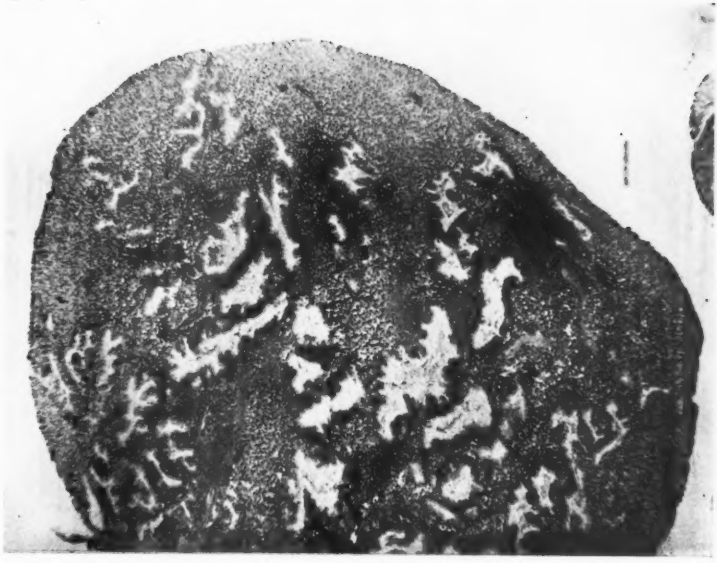

FIG. 11

Endometrium showing dilated irregularly shaped uterine glands and superficial stratum compactum × 40

BL.

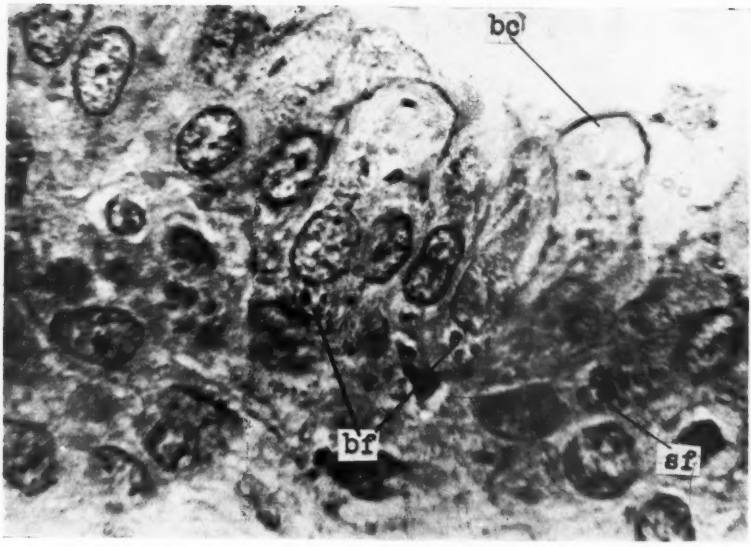

FIG. 12

Endometrium showing basal fat in uterine gland cells. Stained with Sharlach R., counterstained with haematoxylin. × 1200.

bf, globules of fat in base of uterine gland cell; *sf*, stromal cell containing globules of fat.

BL.

the nucleus to one side, and the cell comes to resemble a fat cell. These large vacuoles do not contain fat, but probably are an accumulation of a watery substance which disappears during preparation of the section. In some cases the vacuoles are formed by a sudden rarefaction of a peripheral part in the cytoplasm, and a large vacuole may appear without any fusion of smaller ones. It is possible that the vacuoles represent non-stainable secretion elaborated by the granulosa lutein cells.

Over some of the vacuoles a colloidal substance attached to the vacuole can be seen.

Fibrous core.

Separating the deepest part of the granulosa lutein cells from the central coagulum is a band of fibrous connective tissue. The thickness of this band varies considerably, in some parts it may be 2 mm. thick, and in others it consists only of oedematous connective tissue (Fig. 1, *fb*).

The Fragment of the Ovary.

In the fragment of ovary which was removed with the corpus luteum a number of different structures can be seen.

(1) Small follicular cysts.
(2) Small yellow bodies.
(3) Haemorrhagic bodies.

Small follicular cysts. In the fragment there are 2 follicular cysts one of which measures 3.8 mm. The inner wall of the cyst consists of a thin layer of reticular tissue which represents the basement membrane of the stratum granulosum, and it also separates the latter from the remains of the underlying theca interna. Attached at irregular intervals to this basement membrane are isolated cells of the stratum granulosum. Deep to the reticular membrane there is a fibrous layer which may vary in thickness from 20 to 100 μ. Lying irregularly distributed in and below this membrane are either individual cells or clusters of theca lutein cells. In the majority the nucleus occupies almost the whole of the cell, whereas in others the nucleus represent a quarter of the maximum diameter of the cell and the cytoplasm is water-clear. The theca interna is moderately vesicular in parts, and in others is almost avascular. In this follicle there is no stainable lipoid.

Small yellow bodies. Size of body 4.1 mm. × 2.4 mm. (Fig. 9). The outer surface of this body is formed by compressed

ovarian stroma in which are found a large number of small blood-vessels interspersed at irregular intervals along the periphery of this body (Fig. 9, *fc*).

The centre part consists of loose, sodden tissue which resembles mesenchymal tissue very closely (Fig. 9, *c*). In this tissue are seen a large number of histiocytes containing blood pigment. Some of these histiocytes contain pigment as well as a variable quantity of fat droplets which may vary from 0.1 μ to 2 μ in diameter. In this central area are also fibroblasts with long tapering processes which seem to anastomose with neighbouring cells. The central coagulum contributes about one-quarter to one half of the diameter of the body.

In the peripheral third for three-quarters of the circumference of the body we have a large number of cells which may measure up to 100 μ in diameter. These cells are well separated by the oedematous interstitial tissue containing capillaries. These large cells are choked with lipoid, most of which is in the nature of discrete globules of the order of 1.5 μ in diameter, but amidst these descrete globules there may be a large single, discrete blob of fat about twice the size of the nucleus (Fig. 10). Where this zone merges with the surrounding stroma of the ovary, the fat is scattered in the stroma ovarii, and it is difficult to say whether it is extracellular or not. In the remaining part of the circumference of the body are cells which are probably macrophages (histiocytes) containing incompletely broken-down blood corpuscles. At the junction between this zone containing pigment and the fat-containing cells the macrophages can be seen to contain both broken-down blood corpuscles and droplets of fat.

There are several small yellow bodies which are similar in structure to the one described above, where the fat is diminished and the pigment is scattered in the large histiocytes situated on the periphery, and to a greater extent in the centre of the body.

One of these small bodies, however, calls for a brief description. Its dimensions are 1.7 mm. by 2.1 mm. About half of the circumference of this body is occupied by theca lutein cells, the thickness of this layer varying from 200 μ to 600 μ. The rest of the wall is occupied by an outer zone of fibrosed stroma ovarii along the inner margin of which are a few clusters of surviving theca lutein cells. In the centre of this body are the large pigmented histiocytes separated by a sodden connective tissue matrix. In that part of the body where the theca lutein cells are least developed there is an accumulation of pigmented histiocytes in the false capsule. The thick wall of the theca lutein cells

supported by abundant fibrovascular tissue and the theca lutein cells themselves vary considerably in structure. Some of them have a pale, granular, eosinophilic cytoplasm with a hyperchromatic nucleus situated either in the centre or towards one side of the cell, whereas in others a few surviving cytoplasmic strands are seen suspended in what appears to be a very wet cytoplasm.

Haemorrhagic bodies. In the case of the haemorrhagic bodies —size 1.8 mm. × 1.1 mm.—these were visible to the naked eye as small haemorrhagic structures some of which projected from the surface of the ovary. There was a central cavity lined by irregular patches of cells resembling the stratum granulosum. The central cavity itself is collapsed which may be due to spontaneous rupture or rupture during operation or preparation of the section.

The zone which represents the theca interna is very much thickened (300 μ), and in this zone can be seen a few moderately enlarged cells of the theca interna, but the greatest proportion of the zone is made up of a dilatation of the capillaries or free blood. Fat is extremely scanty in this body, and only a few thecal cells contain any lipoidal droplets in the cytoplasm which is already becoming vacuolated. By far the majority of the theca cells have a size of from 20 to 30 μ; the nucleus is centrally placed and occupies about two-thirds of the cell and the cytoplasm is finely granular and does not contain any vacuoles.

The Endometrium

The endometrium can be divided into a stratum compactum and a stratum spongiosum (Fig. 11). In the compact layer the mouths of the glands are separated by stromal tissue. In the spongiosum there are large numbers of widely dilated, irregular-shaped glands filled with secretion, and the walls show definite tufting.

Stroma.

In the compactum the stromal cells are markedly enlarged and they form a continuous sheet of epithelioid cells closely applied to one another. The nuclei are large and occupy about half of the cell: they are moderately vesicular, and they contain 2 or 3 small nucleoli. Under the low power of the microscope the stroma looks fairly sodden, and under the high power it is seen that this is due to the development of a number of irregular-

sized vacuoles in the cell; these vacuoles may fuse and the nucleus in some cells surrounded by a small rim of cytoplasm is separated from the periphery of the cell by one or more large vacuoles. In addition, it seems as if there is a moderate amount of extracellular oedema and some blood. The oedema is due largely to this intracellular collection of fluid. A few binucleates are present, but mitotic figures are absent.

In the section stained with Sharlach R. it is clear that the vacuolation of the decidual cells is not due to fat, because there is far less fat than there are intracellular vacuoles. Sixty per cent of cells contain a few droplets of fat (Fig. 12). The separation of the glands in the compactum is due chiefly to the enlargement of the stromal cells.

Stratum Spongiosum.

In the stratum spongiosum the stroma may be so highly developed as to separate the glands in some parts, but in most parts the stroma forms only a much attenuated strand of tissue separating the basement membrane of adjacent glands. The stromal cells are smaller than they are in the compactum, some still being spindle-shaped. Unfortunately muscle was not procured so it is impossible to give a full description of the whole extent of the endometrium.

The fat in the deeper parts of the stroma is not as abundant as in the compact layer, being present in 14 per cent of cells. There are a few leucocytes and small round cells lying in the stroma.

The blood-vessels in the stroma, especially in its deeper part, have relatively thick walls as compared with the size of the lumen. The cells in the wall of the vessel have large round, oval nuclei, and the cytoplasm is sodden; and these cells, like the decidual cells in the compact layer of the stroma, look very much like epithelial cells.

Glands.

The surface of the endometrium is lined by cuboidal or low columnar cells; their cytoplasm is vacuolated and some of the cells may contain a few moderately enlarged globules of fat which may lie below or immediately above the nucleus. In the stratum compactum the lumen of the glands is narrow, and the lining epithelium consists of broad, low columnar cells. The

nuclei are moderately chromatic, basal in position, and mitotic figures are absent. The cytoplasm distal to the nucleus is vacuolated. One in three cells contains one or more globules of fat which is found almost exclusively below the nucleus (Fig. 12).

In the middle layers, there is great variation in the size and shape of the cells lining the uterine glands. This is particularly accentuated in the tufts. The shape and size of the cell are determined largely by the stage in the secretory cycle in which any cell may find itself. In this preparation all stages appear between the broad low columnar cell with basal nucleus and the large balloon cell which Sturgis has described as being typical of pregnancy. The ballooning of the cell is a stage in the cycle of secretion of the uterine gland cell. The finely granular cytoplasm of the tall columnar cell becomes very clear, and is, apparently, under considerable tension causing a marked bulging of the distal part of the cell (Fig. 12). In many of the cells which are either of the balloon type or in the process of becoming that type there are a number of angular basophilic bodies which are similar to those seen in Cowper's glands. When the balloon cell liberates its secretion it reverts to the broad low columnar cell, *i.e.* the balloon cell and the broad low columnar cell represent two different stages in the physiological cycle of secretion of the same cell.

In most of the cells the nuclei are either just off the base or lying on the base of the cell. The shape of the nucleus is dependent largely upon local mechanical factors, *i.e.* on the tufts where the cells are compressed the nuclei are mostly elongated.

Thus, this endometrium shows all the characteristic features of the late second half of the cycle including the ballooned cells of Sturgis, and the basal fat in the epithelium of the uterine glands.

Interpretation of Findings

Corpus Luteum.

Gillman and Stein have laid down criteria which they regard as diagnostic of the corpus luteum of pregnancy. These criteria have been arranged to apply to the early and later months of pregnancy. There seems little doubt that the corpus luteum of menstruation, as known to them at that time, can be sharply differentiated from the corpus luteum of pregnancy. Their observations are summarized in Table I. Our persistent functional corpus luteum has been included for comparison.

TABLE I

	Early months	Later months	Pers. Functional C.L.
Cavity	Present	Absent	Coagulum lined by fibrous tissue
Theca lutein cells	Present	Absent	Present
Granulosa lutein cells, lipoid ...	Numerous fine droplets; occasional cells with large discrete droplets filling cell which may contain cholesterol	Diminished; cholesterol-containing cells absent	Present in 90% of cells. The rest the same as early pregnancy
Secretory granules... ...	Numerous	Diminished	Present in 47% of cells
Vacuoles	Very numerous	Greatly diminished or absent	Very numerous
Colloid	Present as small occasional droplets in 6 to 15% of cells. Not calcified	Greatly diminished; larger and more numerous in each cell. May become calcified	Present as small occasional droplets in 2% of cells. Not calcified. 9% precolloid

On comparing our findings with those of Gillman and Stein it is obvious that the only differences between the corpus luteum in the early months of pregnancy and our persistent functional corpus luteum lie in the structure of the centre of the corpus luteum and in the amount and the size of the colloid droplets.

Gillman and Stein have shown that even up to the 4th and 5th months of pregnancy when the central cavity is obliterated central coagulum could not be identified. The obliteration of the cavity is accomplished by the absorption of the fluid and a corresponding increase in the fibrous tissue. In only one case did Gillman and Stein find a central coagulum and that was in an early pregnancy in which the embryo was dead.

Perhaps the amount and distribution of the colloid may be the most distinctive criterion for distinguishing a corpus luteum of the second half of pregnancy from our persistent corpus luteum. In pregnancy the corpus luteum contains large droplets of colloid which are easily recognizable under the low power of the microscope. In the persistent corpus luteum there is abun-

dant precolloid with all intermediate stages to the colloid, but the latter is not very abundant. The precolloid can only be seen under the high power as round or oval granular masses staining blue to orange-red, but always clearly demarcated from the adjacent cytoplasm. The persistent corpus luteum unquestionably contains colloid even though it is present in reduced amounts.

With the possible exception of the amount and size of the colloid droplets and the central coagulum it seems to us to be a difficult matter histologically to distinguish the corpus luteum of early pregnancy from the persistent functional corpus luteum especially when only haematoxylin and eosin staining is used. Both types of corpora have the same general features as shown by the distribution of the lipoids, secretory granules and the colloid, although in the case of the colloid the difference may be appreciated by experienced histologists. Nevertheless, the presence even of some colloid would in the opinion of Portes, Aschheim and Robey make the distinction between these two types of corpora impossible. Gillman and Stein found colloid (0.75 per cent) in a premenstrual corpus luteum, but Miller and Portes, Aschheim and Robey state very definitely that they never found colloid present in the corpus luteum of menstruation in any case.

There is no doubt that the corpora lutea of pregnancy described by Gillman and Stein were from proven cases of intrauterine pregnancy. If later histological evidence should prove that colloid is not found in a sufficiently large number of corpora lutea of menstruation then the histological modifications which occur when the premenstrual corpus luteum develops into a pregnancy corpus luteum are presumably determined by the presence of the embryo. The fact that in our own case corresponding changes in the corpus luteum are not associated with pregnancy would suggest that these reactions may be excited by some hitherto unidentified stimulus not directly related to the presence of a fertilized ovum or an embryo.

Medico-legal Significance.

Portes, Aschheim and Robey from their examination of the corpus luteum of pregnancy claimed that the presence of colloid in the corpus luteum could be used as incontrovertible evidence for the existence of a pregnancy. In fact, they suggest that the presence of this colloid can be used as a medico-legal test for pregnancy. Apart from some of the objections raised by Gillman

and Stein we should like to affirm in addition that it would be extremely hazardous to use this test medico-legally in view of what we have said concerning the persistent functional corpus luteum. Unless we have more definite evidence of pregnancy, such as chorionic tissue or the embryo itself, the medico-legal significance of the presence of colloid must be seriously questioned.

Small Yellow Bodies.

It is a well-known phenomenon that follicles are formed and undergo atresia throughout pregnancy (Schröder,[12] Seitz). The enlargement of the theca cells may be so great that it might be possible in certain cases to regard such atretic follicles, especially when sectioned in such a way that the cavity is not included, as active lutein tissue (Gillman and Stein).

In chorion-epithelioma, the follicles, instead of undergoing atresia, enlarge and may even form massive cysts. Associated with these cysts is the apparent increase in the theca lutein cells.

In the fragment of the ovary associated with this persistent functional corpus luteum different stages from the Graafian follicle to these yellow bodies could be found. In addition, the fact that several of these follicles undergoing atresia are extremely hyperaemic bordering on haemorrhage, indicates that atresia of the follicles leading to the formation of the yellow bodies is a vigorous process and may be initiated by a preliminary haemorrhage. The Graafian follicles, however, never show the same extensive increase in the theca lutein cells as occur throughout pregnancy.

Whereas in the rest of the ovary in pregnancy there is a hormonal substance responsible for producing the growth and atresia of the Graafian follicle, in chorion-epithelioma, however, the follicles do not undergo atresia but form cysts of varying size, all of which are surrounded to a varying extent by masses of theca lutein cells. In the persistent functional corpus luteum the atresia of the follicles is apparently preceded by vascular changes in the theca interna.

In pregnancy, therefore, a hormonal substance is responsible for stimulating the internal thecal cells in the Graafian follicle before it undergoes atresia, in the chorion-epithelioma the stimulus leads to a production of massive follicular cysts, accompanied by increase in the cells of the theca interna but not associated with atresia. In the persistent functional corpus luteum, however, the follicular atresia is rapidly accomplished and it is

preceded by vascular changes and even haemorrhage in the theca interna and only then apparently does follicular atresia occur, associated with the destruction of the stratum granulosum, but accompanied by the enlargement of the thecal cells. Thus there appears to be a significant difference in the reactions in the ovary in pregnancy, chorion-epithelioma and persistent functional corpus luteum.

Endometrium.

Sturgis drew attention to the presence of the large balloon cells in the uterine glands during pregnancy, and claimed that this type of cell was diagnostic of pregnancy. Although these balloon cells have been observed by others during the late second half of the cycle and in pregnancy (Schröder, Bartelmez and Bensley[13]) they have not been regarded as diagnostic of pregnancy. Similarly, in the case which we have described above, these cells were very numerous. It follows, therefore, that the balloon cells are the result of corpus luteum activity rather than of pregnancy.

Basal fat. There is one remarkable feature about the endometrium in this case which is worthy of comment. Aschheim[14] drew attention to the presence of basal granular fat in the gland cells in 80 per cent of endometria taken in the late second half of the cycle, and in all cases of pregnancy. Aschheim thought that this fat was of value in nourishing the embryo and providing essential vitamins. Froboese[15] refuted Aschheim's contention that basal fat was found in early pregnancy; he maintained that basal fat was found only in some cases in the endometrium of the non-pregnant woman, and then only when the degenerative processes immediately preceding menstruation were well advanced. He concluded that the fat was a degenerative process. It has been shown, however, that the development of basal fat is not a degenerative phenomenon, but is related to optimal corpus luteum activity (Gillman[16, 17]). The fact that in this present case we have a corpus luteum the structure of which suggests profound physiological activity, associated with the appearance of endometrial fat, strongly supports the view that the basal fat is in some way related to a functional corpus luteum and is not a product of cell degeneration or haemorrhage.

Decidual reaction. One of the most important reactions occurring in the endometrium in pregnancy is the development of the decidual cell. The decidual cell is developed directly from the stromal cell. The stromal cells in a premenstrual endomet-

rium, so far as we know, do not attain the size of the decidual cells in the first half of pregnancy. The stromal cells in our case had reached a stage of development no greater than that encountered in a well-developed endometrium of the late second half of the cycle, despite the fact that the corpus luteum had been functional for at least 4 months. It appears from these facts, therefore, that the decidual reaction is determined in the ultimate analysis directly by the stimulus emanating from the embryo or the fertilized ovum. The pioneer work of Leo Loeb[18] has shown that, if the endometrium of a rat under the influence of progesterone is traumatized, a deciduoma is produced. The action of progesterone, however, is indispensable to, but not directly responsible for, the decidual reaction. And, therefore, as in our own case despite the fact that there was a very active corpus luteum, the endometrium had only developed to a premenstrual state.

Discussion

Is this corpus luteum physiologically active?

Before we are able to interpret the histological findings of the corpus luteum described in this paper, it is necessary to analyse critically the premenstrual corpus luteum, the degenerating corpus luteum of menstruation, and the corpus luteum at different stages of pregnancy, and also to establish that this body is not a neoplasm.

Premenstrual corpus luteum. The size of the premenstrual corpus luteum is compatible with ours. The central coagulum is much bigger in the premenstrual body. In the premenstrual corpus luteum, further, there is no band of fibrous tissue separating the inner part of the lutein tissue from the central coagulum.

In the premenstrual corpus luteum colloid is absent (or it may be present in up to 0.75 per cent of cells); cells containing granules are present, the presence of scattered cells containing large discrete droplets of lipoid have not been identified; the extent of vacuolation of the lutein cells has not been described as being comparable to that which we saw in our specimen, nor have we encountered such marked vacuolation and large quantities of precolloid in premenstrual bodies.

Therefore, it is unlikely that this is a premenstrual corpus luteum on account of the high percentage of cells containing secretory granules and colloid; the high proportion of cells containing large droplets of lipoid; the presence of the thick band separating the lutein cells from the small coagulum; and finally,

the extreme vacuolation of a large number of granulosa lutein cells.

Degenerating corpus luteum. In the degenerating corpus luteum there is a large peripheral rim of yellow lutein tissue lining the large haemorrhagic central coagulum; almost every lutein cell contains large droplets of lipoid; there is an extreme abundance of cholesterol; but there is an absence of secretory granules, colloid and vacuoles.

A degenerating corpus luteum 6 weeks old shows definite evidence of the degenerative process in the cells themselves; shrinkage of some cells and gross enlargement of others, pyknosis of the nuclei, and diminished vascularity. Therefore, our corpus luteum cannot be a degenerative corpus luteum of menstruation.

Pregnancy corpus luteum. The corpus luteum described above is in many respects almost indistinguishable from one of pregnancy up to the 4th month.

The corpus luteum here fulfils almost all the criteria described for the first half of gestation by Gillman and Stein. The only unusual feature of our corpus luteum is the fact that in none of the corpora lutea of pregnancy, with the exception of Case 1 when the embryo was dead (Gillman and Stein), has a central coagulum been described, however small; but the fibrous band seems to suggest the possibility of the accumulation of considerable quantities of fluid in the corpus luteum at an earlier period of its development.

We have, then, to show that this was not a pregnancy corpus luteum, or that during the 18 weeks of amenorrhoea under consideration, the woman was not pregnant.

The evidence against the presence of a pregnancy in this patient is only circumstantial. The size of the uterus, as already stated, was incompatible with uterine or even ectopic gestation of over 6 weeks. During 18 weeks there was complete amenorrhoea except for an episode of bleeding for one day exactly 14 weeks after the last period.

The objection may be raised that an ectopic pregnancy may have occurred without corresponding to the full period of 18 weeks. There was no evidence on inspection and palpation of the Fallopian tubes that they harboured any pathological tissue. Retrograde insufflation was carried out and the contralateral tube found to be blocked, but this manoeuvre was adopted only on account of the presence of adhesions around the fimbriated ends of the tubes. There is the remote possibility of an abdom-

inal pregnancy. Relative to a secondary abdominal pregnancy it is quite definite that erosion of either tube was not apparent, nor any signs of fresh blood or old clots or adhesions in the deeper part of the pouch of Douglas. Nor, relative to either primary or secondary abdominal pregnancy, was any trace of embryo, foetus, or placenta seen. The possibility of an abdominal pregnancy—a factor which in this type of case could never be absolutely eliminated—calls for some consideration.

Now the period of amenorrhoea offers the following possibilities. There may have been:

(1) Amenorrhoea for 18 weeks due to persistent functional corpus luteum. This is our view.
(2) Pregnancy followed by amenorrhoea due to some unknown cause.
(3) Amenorrhoea due to some unknown cause followed by pregnancy.
(4) Amenorrhoea due to some unknown cause followed by ovulation with formation of the persistent functional corpus luteum.

Concerning (2) in view of the appearance of the stroma in the endometrium, which did not show any decidual reaction, the woman could not have been pregnant, unless the pregnancy endometrium was shed at the 14th week. This would demand a corpus luteum of pregnancy with an age of at least 10 to 12 weeks. Such a corpus luteum of pregnancy could not have been missed at laparotomy. That our corpus luteum was not the one associated with such a pregnancy is shown by the lack of signs of degeneration even to the extent that occurs in ectopic pregnancies in which the number of cells containing secretory granules does not rise above 20 per cent (Gillman and Stein). That our corpus luteum was active is strongly supported by the fact that removal of the corpus luteum was followed by bleeding within 48 hours. Thereafter, the cycle was re-established because the patient bled 27 days later. This means that this corpus luteum discovered on the ovary had most probably inhibited the menstrual rhythm, and that the moment it was removed the menstrual cycle re-established itself once more.

(3) We feel that against this possibility there is the coincidence of pregnancy succeeding some months of unaccountable amenorrhoea in a woman who had never missed a period before, the fact that removal of the only visible corpus luteum was followed by a normal period with profuse loss 29 days after operation, and the absence of a decidual reaction in the endo-

metrial stroma. It cannot be emphasized too strongly that the endometrium shows definitely that there could not have been any live pregnancy at the time of operation.

(4) This possibility is unlikely to be of any significance, because a corpus luteum, other than the one described, was not observed in either ovary. The latter, occupying the outer pole of the ovary, was very obvious and drew attention at once. It seems reasonable to assume, then, that the last corpus luteum to be formed prior to the persistent body had become a corpus albicans which was not visible on the surface, and which would require several months for its formation.

In addition to the suggested evidence against the presence of a pregnancy during the period of amenorrhoea, there is the fact that our corpus luteum had a central coagulum which is not found in the pregnancy corpus luteum. The colloid also showed that this was most probably not a corpus luteum of pregnancy.

And it has been shown that it was not a premenstrual corpus luteum. All the evidence, therefore, points to the fact that this corpus luteum was persistent and functional.

Summary and Conclusions

An account of the microscopic features of the corpus luteum, a fragment of ovary and the endometrium have been described in an authentic case of persistent functional corpus luteum.

Evidence has been adduced from the study of the intracellular lipoids, secretory granules, vacuoles, colloid and the nature of the central cavity to show that this corpus luteum is different histologically from the premenstrual and degenerating corpus luteum of menstruation. It has been shown that this persistent functional corpus luteum resembles in many respects the corpus luteum of pregnancy, but that the colloid droplets were more numerous and attained a greater size during pregnancy and that a central coagulum was present in the persistent functional corpus luteum and is usually absent in pregnancy.

The value of colloid in a corpus luteum as incontrovertible evidence for the existence of a pregnancy has been seriously questioned.

Attention has been drawn to the existence of small, yellow bodies in the fragment of ovary; the significant differences in the reaction of the Graafian follicles in pregnancy, in chorion-epithelioma and in persistent functional corpus luteum have been indicated.

The endometrium exhibited a typical premenstrual reaction

associated with the pregnancy cells of Sturgis. The value of infra-nuclear or basal fat in the gland cells as an indicator of optimal progesterone activity has been emphasized.

It has been shown that the stromal cells in the endometrium had reached a stage of development no greater than that encountered in the endometrium in the late second half of the cycle, despite the fact that the persistent functional corpus luteum had been active for a period of 4 months.

It is suggested that the term "persistent functional corpus luteum" should be applied to conditions similar to the one described above.

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Diabetes Mellitus and Pregnancy

BY

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PREGNANCY in patients suffering from diabetes mellitus is a comparatively rare event. In the last 14 years at University College Hospital only 21 patients with definite diabetes mellitus have been observed in 25 pregnancies. This gives an incidence of 1:930 deliveries, but this is probably a high figure since a number of the cases were referred to the obstetric department from the Diabetic Clinic of the Hospital. In 19 pregnancies, diabetes had been diagnosed and treated by a physician before the onset of pregnancy. In the remaining 6 pregnancies the diagnosis was made during pregnancy on the strength of a fasting blood sugar of 130 mgm. per cent or over, and a typical diabetic blood-sugar curve.

The tendency to atrophy of the genital organs with resulting amenorrhoea was frequently observed in cases of diabetic mellitus in the pre-insulin era. Sterility was, therefore, common. Since the introduction of insulin many cases of amenorrhoea have been successfully treated, even when the amenorrhoea has been of 13 years' duration (Joslin[1]). Likewise the fertility of the diabetic has increased. Nevertheless, pregnancy in the diabetic is still an infrequent occurrence. Certain considerations, however, suggest that this infrequency may not be entirely attributable to the presence of diabetes.

White[2] gives figures which show that the onset of diabetes is twice as common in the fourth decade and four times as common in the fifth decade as in either the first, second or third decade. In 16 of the 21 patients of this series, the age at onset of the diabetes was definitely known, and varied from 22 years to 40 years, the average being 31 years. The average age of these 16 patients when pregnant for the first time while definitely suffering from diabetes was 33.3 years, the youngest pregnant diabetic being 24 years and the oldest 43 years. The fact that diabetes is much commoner in women during the latter part of

the child-bearing period, when pregnancy is less frequent, than during the early part of reproductive life when pregnancy is frequent, must in large part account for the rarity of pregnancy in diabetics.

Parity. Of the 21 patients who became pregnant after developing diabetes mellitus, 12 were primigravidae and 9 multiparae. Of one of the multiparae recently observed throughout her diabetic pregnancy at this hospital, the history of her only previous pregnancy is accurately known. This previous pregnancy ended in the birth of a live infant weighing 9 pounds, 6 months before the clinical onset of the diabetes. This infant died in the neonatal period of a congenital heart lesion. Recently, Allen,[3] from the study of the obstetric records of patients having pregnancies complicated by diabetes and what he calls benign type of glycosuria, has drawn attention to the fact that there is a high incidence of large infants and an increased foetal mortality in pregnancies occurring long before the glycosuria becomes manifest. He suggests that "glycosuria is only another or perhaps later manifestation of a condition that may produce larger babies and sometimes kills them before birth". The obstetric histories of the remaining 8 multiparae in this series are not known accurately except in one other patient. She had had one previous pregnancy which had ended in the birth of a normal live infant, weighing $7\frac{3}{4}$ pounds at term. This delivery occurred 2 years and 7 months before the clinical onset of the diabetes.

Insulin Requirements During Pregnancy

Duncan and Fetter,[4] in a series of 84 diabetic pregnancies collected from the literature, found that the carbohydrate tolerance was diminished in 55.9 per cent, unchanged in 19.1 per cent and increased in 25 per cent. In 6 cases of their own they found that the carbohydrate tolerance was diminished during pregnancy. Brandstrup and Okkels,[5] in a series of 18 diabetic pregnancies treated with insulin, observed that the insulin requirements were increased in 4 (22 per cent), unchanged in 8 (44 per cent) and decreased in 6 (33 per cent). They state, however, that the diabetes of some of their patients was poorly managed or neglected. Skipper[6] found that the insulin requirements were increased as pregnancy advanced in 13 of 18 diabetic pregnancies (72.2 per cent) and in 4 patients were unchanged or decreased.

In the present series of 25 diabetic pregnancies, 4 were

treated with diet alone and 21 with diet and insulin. In one of these 21 cases, the patient discharged herself from hospital at about the 34th week of pregnancy after only 6 weeks' supervision, and in another, abortion occurred at the 16th week of pregnancy. Of the remaining 19 pregnancies, the insulin requirements, as pregnancy advanced, were increased in 14 (74 per cent), unchanged in 4 and decreased in 1. These figures are similar to those of Skipper and support the contention that the carbohydrate tolerance usually diminishes as pregnancy advances. While a review of these cases suggests that there is a true decrease in the carbohydrate tolerance during pregnancy, it must be remembered that in many cases increase or other adjustments in the diet will have affected the insulin requirements.

It has been said that any decrease in the insulin requirements during pregnancy is due to the transference of insulin from the foetus to the mother. Skipper, in the article referred to above, reviews the evidence and concludes that there is no good reason to believe that the improvement in the carbohydrate metabolism, which has occasionally been observed during pregnancy, is due to this cause.

Complications of Pregnancy

Hydramnios. Six cases of clinical hydramnios were observed in the 25 pregnancies, an incidence of 24 per cent. Four of these 6 pregnancies resulted in intra-uterine death of the foetus. In 2 cases there were congenital abnormalities of the foetus which died *in utero*. One case ended in the birth of a live infant at term weighing 11 pounds 10½ ounces.

Coma. Only one case of diabetic coma occurred in the series. This occurred at the 33rd week of pregnancy in a patient who was also hypertensive—Case 6 (see Tables I and III).

Toxaemia of late pregnancy—see Table III. Under this heading are included the following conditions:—

(1) Pre-eclamptic toxaemia.

To be included in this group, a patient must fulfil the following conditions:

(*a*) She should have been healthy before the pregnancy in question and should not have had a previous toxaemic pregnancy or one ending in the birth of a premature or macerated foetus or in abortion.

(*b*) The signs of toxaemia should not have appeared before the 20th week of the present pregnancy.

the child-bearing period, when pregnancy is less frequent, than during the early part of reproductive life when pregnancy is frequent, must in large part account for the rarity of pregnancy in diabetics.

Parity. Of the 21 patients who became pregnant after developing diabetes mellitus, 12 were primigravidae and 9 multiparae. Of one of the multiparae recently observed throughout her diabetic pregnancy at this hospital, the history of her only previous pregnancy is accurately known. This previous pregnancy ended in the birth of a live infant weighing 9 pounds, 6 months before the clinical onset of the diabetes. This infant died in the neonatal period of a congenital heart lesion. Recently, Allen,[3] from the study of the obstetric records of patients having pregnancies complicated by diabetes and what he calls benign type of glycosuria, has drawn attention to the fact that there is a high incidence of large infants and an increased foetal mortality in pregnancies occurring long before the glycosuria becomes manifest. He suggests that "glycosuria is only another or perhaps later manifestation of a condition that may produce larger babies and sometimes kills them before birth". The obstetric histories of the remaining 8 multiparae in this series are not known accurately except in one other patient. She had had one previous pregnancy which had ended in the birth of a normal live infant, weighing $7\frac{3}{4}$ pounds at term. This delivery occurred 2 years and 7 months before the clinical onset of the diabetes.

Insulin Requirements During Pregnancy

Duncan and Fetter,[4] in a series of 84 diabetic pregnancies collected from the literature, found that the carbohydrate tolerance was diminished in 55.9 per cent, unchanged in 19.1 per cent and increased in 25 per cent. In 6 cases of their own they found that the carbohydrate tolerance was diminished during pregnancy. Brandstrup and Okkels,[5] in a series of 18 diabetic pregnancies treated with insulin, observed that the insulin requirements were increased in 4 (22 per cent), unchanged in 8 (44 per cent) and decreased in 6 (33 per cent). They state, however, that the diabetes of some of their patients was poorly managed or neglected. Skipper[6] found that the insulin requirements were increased as pregnancy advanced in 13 of 18 diabetic pregnancies (72.2 per cent) and in 4 patients were unchanged or decreased.

In the present series of 25 diabetic pregnancies, 4 were

treated with diet alone and 21 with diet and insulin. In one of these 21 cases, the patient discharged herself from hospital at about the 34th week of pregnancy after only 6 weeks' supervision, and in another, abortion occurred at the 16th week of pregnancy. Of the remaining 19 pregnancies, the insulin requirements, as pregnancy advanced, were increased in 14 (74 per cent), unchanged in 4 and decreased in 1. These figures are similar to those of Skipper and support the contention that the carbohydrate tolerance usually diminishes as pregnancy advances. While a review of these cases suggests that there is a true decrease in the carbohydrate tolerance during pregnancy, it must be remembered that in many cases increase or other adjustments in the diet will have affected the insulin requirements.

It has been said that any decrease in the insulin requirements during pregnancy is due to the transference of insulin from the foetus to the mother. Skipper, in the article referred to above, reviews the evidence and concludes that there is no good reason to believe that the improvement in the carbohydrate metabolism, which has occasionally been observed during pregnancy, is due to this cause.

Complications of Pregnancy

Hydramnios. Six cases of clinical hydramnios were observed in the 25 pregnancies, an incidence of 24 per cent. Four of these 6 pregnancies resulted in intra-uterine death of the foetus. In 2 cases there were congenital abnormalities of the foetus which died *in utero*. One case ended in the birth of a live infant at term weighing 11 pounds 10½ ounces.

Coma. Only one case of diabetic coma occurred in the series. This occurred at the 33rd week of pregnancy in a patient who was also hypertensive—Case 6 (see Tables I and III).

Toxaemia of late pregnancy—see Table III. Under this heading are included the following conditions:—

(1) Pre-eclamptic toxaemia.

To be included in this group, a patient must fulfil the following conditions:

(*a*) She should have been healthy before the pregnancy in question and should not have had a previous toxaemic pregnancy or one ending in the birth of a premature or macerated foetus or in abortion.

(*b*) The signs of toxaemia should not have appeared before the 20th week of the present pregnancy.

TABLE I.
FOETAL DEATHS.

Case No.	Complication of pregnancy	Control of diabetes in later weeks of pregnancy	Outcome of the pregnancy	Type (and time) of delivery	Weight pounds	Weight oz.	Remarks
1	Unknown	Unknown	" Baby born dead "	Spontaneous (?)	?		No proper antenatal supervision. Patient discharged herself at 34th week of pregnancy after only 6 weeks supervision.
5	Unclassifiable toxaemia. Hydramnios. Puerperal pyrexia (pyelitis)	Balanced	Intra-uterine death (34th week)	Induction of labour, spontaneous (34th week)	5	13½	Foetus macerated. Deformity of left arm.
6	Hypertension Hydramnios	Unbalanced Diabetic coma (33rd week)	Intra-uterine death (33rd week)	Spontaneous (33rd week)	5	7	Death followed coma. Foetus macerated. Abnormality of vessels to lower limbs. Previous pregnancy ended in macerated foetus and complicated by toxaemia (Case 5).
7	Pre-eclamptic toxaemia Hydramnios	Unbalanced	Intra-uterine death (36th week)	Spontaneous (40th week)	?		Foetus macerated.
11	Pre-eclamptic toxaemia Hydramnios	Balanced	Intra-uterine death (29th week)	Spontaneous (30th week)	4	0	Foetus macerated.
12	Nil	Balanced	Abortion (26th week)	——	—		
13	Hypertension	Unbalanced	Abortion (16th week)	——	—		Previous pregnancy (Case 12).
15	Unclassifiable toxaemia	Balanced	Intra-uterine death (36th week)	Spontaneous (40th week)	3	7	Foetus macerated.
21	Unknown	Unknown	Intra-uterine death (39th week)	Spontaneous (40th week)	9	2	Incomplete antenatal records. Foetus macerated.
23	Unknown	Unknown	Intra-uterine death (38th week)	Spontaneous (42nd week)	8	14	Incomplete antenatal records. Foetus macerated.
25	Pre-eclamptic toxaemia	Balanced	Intra-uterine death	Spontaneous	6	14	Foetus macerated.

(*c*) There should be evidence of pre-eclamptic toxaemia of the following nature: A blood-pressure over 130/70 mm. Hg with or without any of the usual accompanying signs such as albuminuria or oedema.

Seven of the 25 pregnancies were complicated by pre-eclamptic toxaemia.

(2) Hypertension.

In this group are included the patients who were hypertensive before the pregnancy began or who were found to have a blood-pressure over 130/70 mm. Hg when first seen, provided this was before the 20th week of pregnancy. Three patients came into this group. One of these 3 aborted at the 16th week, so that she cannot be included in the class of toxaemia of late pregnancy.

(3) Recurrent toxaemia.

In order to be included in this group, a patient should have had a previous toxaemic pregnancy but should have been free from hypertension or evidence of chronic nephritis previous to the present pregnancy. The signs of toxaemia should not have appeared before the 20th week of the present pregnancy.

Only one patient is known to have had a previous toxaemic pregnancy. She was, however, hypertensive before the onset of the pregnancy in question and is, therefore, included in the hypertensive group.

(4) Eclampsia.

Eclampsia did not complicate any pregnancy in the series.

(5) Unclassifiable toxaemia.

This group includes cases of toxaemia which cannot be included in the above groups and which are not complicated by chronic nephritis. The 2 cases of the series included under this heading were excluded from the other groups because the patients were first seen so late in their pregnancies that reliable information could not be obtained as to the time of onset of their toxaemia.

Excluding the one complicated by hypertension that ended in abortion before the 20th week, there were, therefore, 11 pregnancies out of a total of 24, which were complicated by toxaemia of late pregnancy, an incidence of 45.8 per cent. Seven of these came into the group of pre-eclamptic toxaemia based on the above standards, an incidence of 29.2 per cent.

In a series of 1864 recent consecutive deliveries of patients attending this hospital, a sixth of whom were delivered in their own homes, 664 of the pregnancies were complicated by toxae-

mia of late pregnancy, an incidence of 36 per cent. Four hundred and ninety-two of these came into the group of pre-eclamptic toxaemia, an incidence of 26.6 per cent. Priscilla White[7] states that toxaemia and eclampsia are almost 50 times as common in diabetic pregnancies as in otherwise normal pregnancies. This comparison is apparently based on the relative incidence of eclampsia which, in another article previously mentioned,[2] she gives as 13 per cent for the young pregnant diabetic and 0.3 per cent for the pregnant non-diabetic. Mengert and Laughlin[25] found that non-convulsive toxaemia was 3 times as common in their series of 33 diabetic pregnancies as compared with the general incidence for the entire obstetric service during the year 1937. The figures obtained from this small series of diabetic pregnancies and from the series of non-diabetic pregnancies at this hospital do not bear out the contention that the incidence of toxaemia of late pregnancy (and pre-eclamptic toxaemia) in diabetic patients is much higher than in non-diabetics.

Methods of Delivery

Two of the 25 pregnancies ended in abortion at the 26th and 16th week of pregnancy. These two abortions occurred in the same patient, an interval of about 3 years intervening between the pregnancies. Of the remaining 23 pregnancies, 12 went to term, 10 being delivered normally, one needing to be delivered by the forceps and one having a Caesarean section. Ten were delivered prematurely, 3 spontaneously, one by artificial induction and 6 by Caesarean section. The exact time of delivery of the 23rd patient, who was delivered at home, is unknown. Owing to the large number of intra-uterine deaths occurring after the 36th week of pregnancy, it has usually been the practice at this hospital in recent years to deliver the pregnant diabetic by Caesarean section at the end of the 36th week of pregnancy. Titus[8] states that "the baby is so very important in the severe diabetics and in the 'insulin mother' that, to avoid intra-uterine death, the safest method is Caesarean section when the baby seems quite big enough." He points out, however, that the method of delivery must be individualized.

Maternal Prognosis

The maternal mortality in pre-insulin days was high. Offergeld[9] gives the immediate mortality as 30 per cent rising to 50 per cent 2½ years after delivery. Whitridge Williams[10] gives

similar figures, the immediate mortality being 27 per cent rising to 50 per cent after 2 years. Since the introduction of insulin, the maternal mortality has been considerably reduced. Skipper gives the figure of 9.3 per cent for the immediate mortality with an additional 3.4 per cent for the following 2 years. In this present series of 25 pregnancies in 21 diabetic patients there were no immediate maternal deaths. In each case the management of the pregnancy has been shared with a physician—an important point in the treatment of these patients which has been stressed repeatedly by many writers.

Two of the pregnancies were followed by puerperal pyrexia. In one case this was due to pyelitis and in the other probably to puerperal sepsis but this was not definitely established by bacterial investigation. Brandstrup and Okkels have drawn attention to the danger of pruritus vulvae as a predisposing cause of puerperal sepsis. In addition the diabetic is especially liable to infection of one kind or another. Provided that the diabetes is kept under proper control, pruritus vulvae does not occur and the tendency to infection is reduced to a minimum.

Skipper states that pregnancy does not increase the severity of the diabetes provided that this is well treated. Walker[11] is of the same opinion. In 18 of the 21 pregnancies in which insulin was given during pregnancy, the carbohydrate tolerance before and after pregnancy was known. Following 14 (77.7 per cent) of these 18 pregnancies, the degree of carbohydrate tolerance was unchanged as compared with the pre-pregnant condition. Following the remaining 4 pregnancies, however, the carbohydrate tolerance was diminished.

The first of these cases (Case 10) was a multipara of 26 years, who had had diabetes for at least 3 years before the pregnancy in question. The diabetes had been controlled by a high carbohydrate diet of 1640 calories a day and no insulin before the pregnancy. Subsequent to the pregnancy she was balanced on a high carbohydrate diet of 1640 calories and 30 units of insulin a day.

The second case (Case 18) was a primigravida of 35 years. The onset of the diabetes occurred one year before the commencement of pregnancy and had been controlled by a high carbohydrate diet of 1250 calories a day and no insulin during the 4 months immediately preceding the onset of pregnancy. Following the pregnancy she was balanced on a high carbohydrate diet of 1500 calories and 25 units of insulin a day.

The third case (Case 19) was a multipara of 31 years. The

diabetes had been diagnosed 4 months prior to the commencement of the pregnancy in question and had been controlled by a 10 line diet (Lawrence) and 8 units of insulin a day. After the pregnancy the diabetes was controlled by a high carbohydrate diet of 2000 calories and 35 units of insulin a day.

In the fourth case, a multipara of 33 (Case 2), the onset of diabetes occurred during pregnancy. At about the 20th week of pregnancy she developed symptoms of diabetes—excessive thirst, polyuria and pruritus vulvae—and glycosuria was discovered. The fasting blood sugar was 205 mgm. per cent and the blood-sugar curve was typical of a diabetic. She was balanced on a high carbohydrate diet of 1700 calories and 40 to 50 units of insulin a day during the pregnancy. When last seen, 10 weeks after the delivery, she was balanced on a high carbohydrate diet of 1250 calories and 30 units of insulin a day.

Real conclusions cannot be drawn from these 4 cases, but the observations made in the majority of the patients in this series lend support to the view that pregnancy does not increase the severity of the diabetes provided that this is well treated.

Foetal Mortality

The foetal mortality for pregnancies complicated by diabetes has remained persistently high in spite of the great advance made in the treatment of this disease. The foetal mortality in the pre-insulin era was 41 per cent (Whitridge Williams). Since the introduction of insulin the foetal mortality has remained at approximately the same level and is given as 45 per cent by Skipper.[6] The total foetal mortality is made up of abortions, dead births, still-births and neonatal deaths. In this present series the total foetal mortality was 44 per cent.

The cause of foetal death in diabetic pregnancies is little understood. Abortion has been thought to be due to a deficiency of the glycogen of the endometrium, or an acidosis or a condition of hyper-prolanaemia. Intra-uterine death has been attributed to coma, diabetic or hypoglycaemic, but more commonly the former, or to toxaemia. Congenital malformation or hypoglycaemic coma or asphyxia have been held responsible for neonatal deaths.

Joslin states that there is evidence to show that mild toxaemia in pregnant diabetics antedates the onset of intra-uterine death of the foetus in nearly 80 per cent of the cases. White[12] *et al.*, from a recent study of 35 pregnancies in diabetic women,

draw attention to the association of the death of the viable foetus, premature delivery and neonatal death with the condition of pre-eclamptic toxaemia. From their case-table it would appear that this term is used in a wide sense and corresponds to the whole group of toxaemia of late pregnancy described above. Their study was biochemical rather than clinical, and based on the work of Smith and Smith.[13, 14, 15] These two workers have reported on the study of serum prolan and oestrin in the last 3 months of pregnancy and state that there is an excess of serum prolan and a deficiency of serum oestrin in pre-eclamptic toxaemia and eclampsia as compared with normal pregnancy; they state that these changes occur some 6 weeks before the toxaemia is recognizable clinically. Taylor and Scadron[16] have also studied the serum prolan in late pregnancy but conclude that the general average and range of the prolan concentration of the serum of toxaemic patients were not significantly different from those of normal controls. Selection of the severer types of pre-eclamptic toxaemia resulted in the isolation of a group in which, however, the serum prolan was a little high. White *et al.*, from their investigation of pregnancies in diabetic patients, concluded that the foetal mortality, premature delivery and neonatal death were related to a hyper-prolanaemia. On the advice of Smith and Smith they attempted to reduce the foetal mortality in pregnant diabetics by treating those patients whom they believed to have hyper-prolanaemia with massive hormone therapy. In their series of 9 cases so treated, as compared with a group of 10 untreated cases with hyper-prolanaemia, the foetal mortality was reduced from 60 per cent to 11 per cent. Caesarean section at the 34th to the 38th week of pregnancy was used as the method of delivery in most of their cases both treated and untreated. Since the majority of intra-uterine deaths of the viable foetus occur after the 34th week (6 out of 9 in the present series —see Table I), it seems probable that this disaster to the foetus was avoided by this measure in a number of their cases. It is, therefore, difficult to assess the real value of the hormonal therapy in these circumstances. Further trial of this therapy is needed in pregnancies which are allowed to go to term.

Two of the 25 pregnancies of the present series ended in abortion. Both abortions occurred in the same patient, an interval of about 3 years intervening between the 2 pregnancies. The first pregnancy ended in abortion at the 26th week (Case 12 —see Table I). Not any complication was observed during this pregnancy. The second pregnancy ended in abortion at the 16th

week and was complicated by mild benign hypertension and the diabetes was unbalanced prior to the abortion (Case 13—see Table I).

Nine pregnancies resulted in intra-uterine death of the foetus, which was then delivered macerated.

Neonatal death of an infant did not occur in this series. The total foetal mortality was, therefore, 11 in 25 pregnancies, i.e., 44 per cent (see Table I).

Of the 9 pregnancies ending in intra-uterine death of the foetus, 3 had incomplete antenatal records so that there are no data of any complication occurring during the pregnancy. One of these 3 patients had only 6 weeks' supervision, as she discharged herself from our care when about 34 weeks pregnant. She was subsequently delivered at home of a dead-born foetus. In the remaining 6 cases there was one type or other of toxaemia of late pregnancy and 2 of these 6 cases were unbalanced in the later weeks of pregnancy. Two had pre-eclamptic toxaemia, which appeared at the 29th and 31st week of pregnancy with intra-uterine death of the foetus occurring at the 29th and 33rd weeks respectively. One other had pre-eclamptic toxaemia which appeared at the 30th week with intra-uterine death of the foetus at the 36th week. The diabetes of this patient was unbalanced prior to the death of the foetus. One had benign hypertension and at the 33rd week went into diabetic coma. Intra-uterine death of the foetus, which had congenital abnormality, occurred at this time. The remaining 2 cases had unclassifiable toxaemia, which was noted at the 28th and 36th week. Intra-uterine death of the foetûs, one of which had a congenital deformity, occurred at the 34th and 36th week respectively.

It has not been possible in every case to check whether the diabetes was controlled throughout pregnancy, but an attempt has been made to correlate the control of the diabetes in the later weeks of pregnancy with the outcome of the pregnancy (see Table II). In 2 cases, otherwise well balanced, there were hypoglycaemic symptoms just prior to successful Caesarean section.

It will be seen that in 4 cases, despite control of the diabetes, foetal death occurred. These patients (Cases 5, 11, 15 and 25) all had toxaemia of late pregnancy. One abortion occurred at the 26th week of pregnancy in a balanced patient (Case 12). Of the 4 unbalanced patients, 1 (Case 3) was delivered spontaneously at term of a live infant, and 2 (Cases 6 and 7) were delivered of macerated foetûs. Both of these pregnancies were

TABLE II.

Control of the diabetic in later weeks of pregnancy	Outcome of the pregnancy			
	Alive	Dead	Abortion	Total
Balanced	13 { 8 Caesarean section, 5 spontaneous }	4	1	18
Unbalanced	1 spontaneous	2	1	4
Uncertain	——	3	–	3

complicated by toxaemia and one patient went into diabetic coma prior to intra-uterine death of the foetus. The fourth patient (Case 13) had an abortion at the 16th week of pregnancy which was complicated by mild hypertension.

In Table III are shown the pregnancies known to be complicated by toxaemia of late pregnancy, 12 in number, occurring in the series of 25 diabetic pregnancies at University College Hospital. Excluding Case 13 in which the pregnancy, complicated by mild hypertension and ketosis, resulted in abortion before the 20th week, there were 11 diabetic pregnancies complicated by toxaemia of late pregnancy. Six of these 11 pregnancies resulted in intra-uterine death of the foetus. In 2 of these 6 pregnancies, the diabetes was unbalanced in the later weeks; in one the foetal death was probably related to the diabetic coma rather than the toxaemia, and in the other to the combination of ketosis and toxaemia. Hence in 4 of the remaining 9 toxaemic and balanced diabetic pregnancies, foetal death occurred, an incidence of 44.4 per cent. The remaining 5 toxaemic pregnancies ended in the birth of live infants. One infant (Case 9) might have been saved by the termination of pregnancy at the 36th week by Caesarean section. The toxaemia in the other 4 pregnancies was very mild and 2 were terminated at the 36th and 38th week of pregnancy by Caesarean section.

Browne and Dodds,[17] in a review of cases of toxaemia of late pregnancy at University College Hospital, report the total foetal mortality (which includes abortions, dead births, still-births and neonatal deaths) in 144 cases of pre-eclamptic toxaemia of 13 per cent. In 86 cases of hypertension the total foetal mortality was 38 per cent, but they suggest that it should be more like 25 per cent with the more recent methods of diagnosis and treatment. The total foetal mortality in 193 cases of recurrent tox-

TABLE III.

DIABETIC PREGNANCIES COMPLICATED BY TOXAEMIA OF LATE PREGNANCY.

Case No.	Type of toxaemia	Condition: Time, weeks	Condition: Oedema	Condition: Albumin	Condition: Blood-pressure	Control of diabetes	Outcome	Type of delivery	Weight lb.	Weight oz.	Remarks
5	Unclassifiable toxaemia	28th 33rd	Nil F + L + A B	Nil +	132/96 180/118	Balanced	Intra-uterine death (34th week)	Induction of labour (34th week) macerated	5	13½	Following this pregnancy patient found to be hypertensive. Blood-pressure 144/90 to 186/110
6	Hypertension	12th 28th 32nd	Nil Nil Nil	Nil Nil Nil	130/70 132/90 154/98	Unbalanced Diabetic coma (33rd week)	Intra-uterine death (33rd week)	Spontaneous macerated (33rd week)	5	7	Previous pregnancy Case 5
7	Pre-eclamptic toxaemia	22nd 30th 34th 34th 36th 36th	Nil Nil F L F + L +	Nil Nil Nil Nil	120/70 140/90 155/100 170/100	Unbalanced	Intra-uterine death (36th week)	Spontaneous macerated (40th week)		?	
9	Pre-eclamptic toxaemia	23rd 29th 35th 35th 36th 36th	Nil Nil F L F + L + Face	Nil Nil Nil +	110/70 122/78 134/72 150/100	Balanced	Live infant	Caesarean section (36th week)	5	8	Foetus probably saved by early termination
10	Hypertension	18th 30th 36th 39th	Nil Nil Nil Nil	Nil Nil Nil Nil	130/68 128/68 130/80 130/84	Balanced	Live infant	Spontaneous (40th week)	9	5	Blood-pressure of 140/90 noted before this pregnancy. Very mild toxaemia. Previous pregnancy ended in macerated foetus. Case 23 (Table 1)
11	Pre-eclamptic toxaemia	27th 29th	Nil Nil	Nil Nil	104/68 130/80	Balanced	Intra-uterine death (29th week)	Spontaneous macerated (30th week)	4	0	Early onset of toxaemia

TABLE III (continued)

11	Pre-eclamptic toxaemia	29th	Nil	Nil	130/80	Balanced	death (29th week)	macerated (30th week)	4	0	Early [illegible]

TABLE III (continued)

Case No.	Type of toxaemia	Condition: Time, weeks	Oedema	Albumin	Blood-pressure	Control of diabetes	Outcome	Type of delivery	Weight lb.	Weight oz.	Remarks
15	Unclassifiable toxaemia	36th	Nil	Nil	145/90	Balanced	Intra-uterine death (36th week)	Spontaneous macerated (40th week)	3	7	Subsequent pregnancy 1 year later. No toxaemia. Caesarean section 36th week. Live infant (Case 16)
17	Pre-eclamptic toxaemia	30th	Nil	Nil	122/70	Balanced	Live infant	Caesarean section (38th week)	7	2	Came into class of toxaemia at 33rd week only
		33rd	Nil	Nil	136/70						
		35th	Nil	Nil	110/68						
		38th	Nil	Nil	114/68						
18	Pre-eclamptic toxaemia	10th	Nil	Nil	120/68	Balanced	Live infant	Spontaneous (40th week)	7	9	Mild toxaemia. Mild degree of diabetes controlled by diet alone before onset of pregnancy
		28th	Nil	Nil	110/68						
		32nd	Nil	Nil	140/85						
		36th	Nil	Nil	130/80						
		38th	Nil	Nil	130/70						
20	Pre-eclamptic toxaemia	22nd	Nil	Nil	120/80	Balanced	Live infant	Caesarean section (36th week)	5	13	Mild toxaemia
		28th	Nil	Nil	116/80						
		33rd	Nil	Nil	130/68						
		34th	F	Nil	130/80						
			L								
25	Pre-eclamptic toxaemia	18th	Nil	Nil	126/70	Balanced	Intra-uterine death (33rd week)	Spontaneous macerated (35th week)	6	14	
		22nd	Nil	Nil	130/66						
		27th	F	Nil	126/76						
			A								
		31st	F	+	130/80						
			A								
		32nd	F +	+	144/80						
			L								
			A								
		33rd	F +	+	146/80						
			L								
			A								
13	Hypertension	10th	Nil	Nil	130/80	Unbalanced	Abortion (16th week)	—	—		Previous pregnancy uncomplicated. Resulted in abortion at 26th week. Case 12 (Table 1). Owing to early abortion does not really come into class of toxaemia of late pregnancy

A = Abdominal wall B = Back F = Feet L = Legs

aemia, which includes some of the cases in other groups, was 20 per cent. In 48 cases of eclampsia, the total foetal mortality was 48 per cent. Except for cases of eclampsia, the total foetal mortality for cases of toxaemia of late pregnancy is, therefore, considerably less than the minimal figure of 44.4 per cent for cases of diabetic pregnancies complicated by toxaemia obtained from the series under review. Toxaemia in the diabetic patient, therefore, seems to be a much more serious affair for the life of the foetus than is toxaemia in the non-diabetic. The foetal mortality from toxaemia in diabetics is at least about twice that from toxaemia in otherwise normal patients. This is not accounted for by ketosis.

Table IV shows the outcome of the diabetic pregnancies complicated and uncomplicated by toxaemia of late pregnancy. Four cases had incomplete obstetric records so that there are no data of this complication occurring. It will be seen that there were 9 diabetic pregnancies uncomplicated by toxaemia. Only one of these 9 pregnancies resulted in disaster for the foetus. This pregnancy ended in unaccountable abortion at the 26th week. The remaining 8 pregnancies terminated in the delivery of live infants. Five of these went to term, 3 being delivered *per vias naturales*, one needing the use of the forceps and one being delivered by Caesarean section. The other 3 pregnancies were terminated prematurely by Caesarean section. The diabetes of only one of the 9 patients was unbalanced in the later weeks of pregnancy and she was delivered by the forceps at term of a live infant.

TABLE IV.

Complication of pregnancy	Outcome of pregnancy			
	Alive		Dead	Abortion
Toxaemia	5	3 Caesarean sections 2 spontaneous	6	1*
No toxaemia	8	4 Caesarean sections 4 spontaneous	–	1
Unknown	1 spontaneous		3	–

* Abortion before the 20th week of pregnancy. Mild hypertension complicated the pregnancy.

Congenital Defects of the Foetus

Comyns Berkeley[18] *et al.* state that congenital abnormalities of the child have been reported in 3 per cent of the collected cases of diabetic pregnancies. There were 3 pregnancies in the present series in which some foetal abnormality, other than gigantism, occurred. One infant had a congenital heart lesion but survived. The other 2 foetûs died *in utero* and were born macerated; one had a deformity of one arm and the other an abnormality of the vascular supply to the lower limbs. Both these pregnancies were associated with toxaemia and with hydramnios.

The cause of the high incidence of congenital defects in foetûs delivered of diabetic mothers is not known. Naturally enough, hyperglycaemia of the expectant mother has been blamed both for the congenital defects and for the formation of giant foetûs. In the series of 35 cases of White *et al.*, previously referred to, 3 infants were born alive with congenital defects, an incidence of 8 per cent. All these resulted from pregnancies associated with the condition of hyper-prolanaemia. In the present series, toxaemia was associated with 2 of the 3 pregnancies that resulted in congenitally defective infants. It seems probable, however, that the association was related more to the intra-uterine death of the foetus that occurred in these 2 cases than to the congenital abnormalities. Congenital defects of the foetus usually originate in the early weeks of pregnancy and are, therefore, unlikely to be influenced by toxaemia of late pregnancy.

The same authors suggest that the "tendency to gigantism may be related to (the) abnormal hormone picture (of the pregnant diabetic)". Of the diabetic pregnancies observed at University College Hospital there were 5 in which a large foetus was observed clinically during pregnancy and which resulted in infants weighing more than 9 pounds at term. Of these 5 pregnancies, 4 resulted in live infants and one in intra-uterine death of the foetus 3 days before delivery. Only one of these 5 pregnancies was definitely associated with toxaemia, which was of a very mild degree (Case 10, see Table III). In one other, ending in the intra-uterine death mentioned, the antenatal record is inadequate so that no data are at hand reporting any complication of the pregnancy (Case 21, see Table I).

HYPOGLYCAEMIA

Hypoglycaemia was not observed in any of the live infants. Blood-sugar estimations were performed at delivery and during the neonatal period on only 2 of the 14 live babies, both of which were delivered by Caesarean section at the 36th week. In one case the maternal blood sugar at the time of delivery was 177 mgm. per cent while the infant's was 134 mgm. per cent, this latter figure falling to 97 per cent after 7 hours. In the second case, the maternal and infant's blood sugars were 147 mgm. per cent and 96 mgm. per cent respectively at delivery. This infant's blood sugar rose to 128 mgm. per cent in 24 hours. This rise was probably due to the feeding of the infant with sugar.

The problem of hypoglycaemia in the neonatal period has attracted much attention since it has been held responsible for neonatal death. The hypoglycaemic state of the infant is considered to be due to an overactive foetal pancreas which may be manifested in the form of hyperplasia of the islands of Langerhans (Wilder[19]). Hyperplasia of the islet tissue in infants of diabetic mothers has been reported by a number of observers including Gordon,[20] Gray and Feemster,[21] Brandstrup and Okkels[22] and more recently by Helwig,[23] who found that this hyperplasia was particularly marked in those infants with large birth weights. It is suggested that the stimulus for this hyperplasia is the maternal hyperglycaemia which may act directly or indirectly on the pancreas of the foetus (Gray and Feemster,[21] Brandstrup and Okkels[22]). White[7] states that hypoglycaemia in the infant may be the result of an overdose of insulin to the mother at the time of delivery. In such cases the hypoglycaemia induced in the new-born infant must make its appearance in the first few hours of life and be of short duration. Whatever the cause of the hypoglycaemia, it is desirable to give these infants extra sugar in the early days of neonatal life to counteract the possibility of this complication. Daoud,[24] from a study of the human milk in lactating diabetic women, concludes that the amounts of lactose and other constituents of the milk remain within the range for normal individuals and that glucose is not secreted in the milk of lactating diabetics regardless of the existence or absence of hyperglycaemia. It, therefore, follows that it is desirable to give extra sugar to the infant whether it is being artificially fed or breast fed.

Conclusions

The incidence of late toxaemia of pregnancy in diabetic expectant mothers does not appear to be much higher than that in otherwise normal expectant mothers as judged by the review of this small series of cases.

The prognosis as regards life for the pregnant diabetic is good and pregnancy does not increase the severity of the diabetes provided that this is well treated.

The prognosis for the foetus, on the other hand, is poor in spite of the great advance made in the treatment of diabetes. Foetal death can occur even in the absence of ketosis, but ketosis probably increases the risk to the foetus, especially if it is severe and diabetic coma occurs.

Toxaemia appears to be a potent cause of intra-uterine death of the viable foetus in the pregnant diabetic. The foetal mortality from toxaemia in diabetics is, at least, about twice that from toxaemia in otherwise normal patients. This cannot be accounted for by an associated ketosis.

Until further information on the causes of the high foetal mortality in diabetic pregnancies is obtained and adequate treatment instituted, it seems reasonable to suggest that the pregnant diabetic should be managed on the following lines:

1. The care of the patient should be shared with a physician who will supervise the treatment of the diabetes. The diabetes must be well balanced and ketosis and the onset of diabetic coma and hypoglycaemic coma should be avoided at all costs. Chills and infections are predisposing causes of diabetic coma and should be avoided so far as it is possible to do so. Teeth and other possible foci of sepsis should receive attention.

2. Adequate antenatal supervision must be given so that the first signs of toxaemia of late pregnancy may be observed as early as possible and treatment instituted in hospital.

3. The foetus should be X-rayed in the later weeks of pregnancy to exclude any gross foetal abnormality which is incompatible with survival after delivery, and which can be detected by this procedure. This precaution may save an unnecessary Caesarean section.

4. Method of delivery.

In those cases that are not complicated by toxaemia or have only a very mild degree such as a slight elevation of the blood-pressure (see Table III), the patient should be allowed to go

to term and delivered *per vias naturales* (or Caesarean section if the size of the foetus necessitates this).

When the pregnancy is complicated by more than a very mild degree of toxaemia and the X-ray does not show any gross abnormality incompatible with survival after delivery, Caesarean section should be performed when the maturity and size of the foetus is considered compatible with survival. This time is usually about the 36th week of pregnancy. In the elderly primigravida it is perhaps preferable to select Caesarean section as the method of delivery rather than run the risk of obtaining a dead foetus delivered *per vias naturales*.

In all patients, whatever the method of delivery selected, the diabetes must be carefully controlled during the labour or Caesarean section.

5. During the puerperium it is advisable to give the infant extra sugar so that any tendency to hypoglycaemic coma is eliminated.

Summary

1. A series of 25 diabetic pregnancies in 21 patients are reviewed.

2. The average age of the patients when the onset of the diabetes occurred was 31 years. The average age when pregnant for the first time while suffering from diabetes was 33.3 years. It is suggested that the tendency for the onset of the diabetes to occur in the latter part of the child-bearing period is largely responsible for the comparative rarity of pregnancy occurring in the diabetic.

3. The insulin requirements were increased as pregnancy advanced in 74 per cent of the cases.

4. The maternal prognosis is good and pregnancy does not make the diabetes worse provided that this is well treated.

5. The incidence of toxaemia of late pregnancy in pregnant diabetics is not much higher than in non-diabetics.

6. The foetal mortality was 44 per cent. It is suggested, from the review of this small series, that toxaemia of late pregnancy is a potent cause of intra-uterine death of the viable foetus and is twice as lethal to the foetus of the pregnant diabetic as to the foetus of the non-diabetic expectant mother.

7. Congenital deformities, gigantism and hypoglycaemia are briefly reviewed. The advisability of giving extra sugar to the new-born infant of the diabetic is stressed.

8. The management of the pregnant diabetic suggested by this review is outlined.

I wish to express my gratitude to Professor F. J. Browne, Director of the Obstetric Unit, for his helpful advice and permission to make use of the case records of the Obstetric Unit; to Professor H. P. Himsworth, Director of the Medical Unit, for permission to make use of the records of the Diabetic Clinic and for reviewing this paper; and to Dr. M. L. Rosenheim for his help with regard to the condition of the diabetes of the cases.

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Renal Function Tests in Normal and Toxaemic Pregnancy

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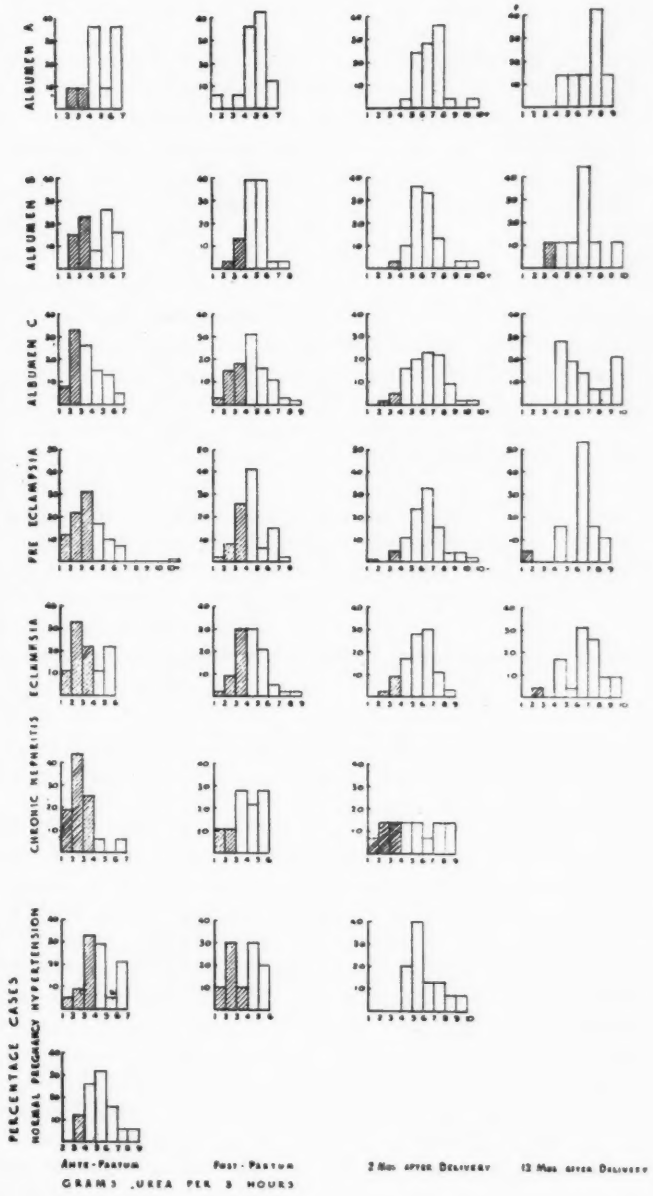
DURING a comprehensive investigation of various aspects of the toxaemias of pregnancy, a large number of renal function tests have been performed on patients during and after a toxaemic pregnancy. Information regarding a number of problems has been collected and three aspects have been chosen for discussion in this paper. In the first instance the results of tests for renal efficiency during, and at different times after, toxaemic pregnancy are compared and the value of individual tests in relation to the management of the present and subsequent pregnancies is discussed. Secondly, the investigation has revealed certain new facts in relation to the assessment of kidney function, during and after normal toxaemic pregnancy, when tested by means of the urea concentration-excretion test.[1] Finally, the statement that renal function tests during the puerperium are useless for prognosis has been investigated.

The conclusions deducted in regard to these problems have been drawn from the study of 3,000 tests for renal efficiency during and after toxaemic pregnancy. The patients have been classified into 7 groups, depending on the type of toxaemia which is defined according to the method customary in this hospital.

The groups of toxaemia are:

1. Albuminuria of pregnancy which for the purposes of this investigation has been subdivided into three types:

(*a*) Albuminuria A, in which albumin is observed on one day only.


ALBUMEN A
ALBUMEN B
ALBUMEN C
PRE ECLAMPSIA
ECLAMPSIA
CHRONIC NEPHRITIS
HYPERTENSION
NORMAL PREGNANCY
PERCENTAGE CASES
ANTE-PARTUM
POST-PARTUM
2 MON. AFTER DELIVERY
12 MON. AFTER DELIVERY
GRAMS UREA PER 3 HOURS

K.

(*b*) Albuminuria B, in which albumin persists for not longer than 4 days.

(*c*) Albuminuria C, when albumin is present for longer than 4 days and in some instances is associated with either raised blood-pressure or oedema, or both of these conditions.

2. Pre-eclampsia—in addition to persistent albuminuria, raised blood-pressure and oedema. These patients suffered from one or more of the following symptoms:—headache, visual disturbances, epigastric pain, vomiting.

3. The eclamptic group included only those patients who had typical eclamptic fits.

4. Chronic nephritis. These patients showed some evidence of permanent renal damage. They showed break-down in kidney function earlier in pregnancy than is customary in other toxaemias. This break-down was characterized by early rise in blood-pressure and persistence of raised blood-pressure, oedema and albuminuria, together with symptoms such as headache, vomiting and eye signs.

5. Hypertension. This group of patients was characterized by a temporary rise in blood-pressure associated with some of the symptoms specified in chronic nephritis, but responded quickly on completion or termination of the pregnancy.

6. Accidental haemorrhage.

7. Miscellaneous—including pyelitis, post-partum haemorrhage, and hyperemesis.

A. Value of Renal Function Tests in Relation to Management of the Present and Subsequent Pregnancies.

It has previously been shown that the blood urea, urea concentration-excretion and the Fowweather urea clearance tests form a useful combination for the determination of renal efficiency.[2] These tests, in conjunction with qualitative and quantitative tests for albumin, have been performed on patients before delivery and 8 days, 2 months and 12 months after delivery. It was not possible to obtain tests on every patient at each of these times, but in 330 patients, tests 2 months after delivery have been obtained following tests performed either before delivery or 8 days post-partum. In 93 instances tests were obtained at both of these times and also 2 months after delivery. Eighty-one patients returned for tests 12 months later. The numbers and types of tests in each of the toxaemias are correlated in Table I.

Results of Individual Tests.

1. *Blood Urea Test.*

All the 348 blood urea tests obtained from 147 patients in the normally pregnant, mildly toxaemic (albuminuria A & B), hypertensive, accidental haemorrhage and miscellaneous groups of patients were normal. The tests included 65 tests before delivery, 104 in the puerperium and 179 tests at least 2 months after delivery. Among those patients with persistent albuminuria C, the blood urea was raised in 4 of the 42 tests during pregnancy. In 2 of these patients the blood urea was still increased in the puerperium but had become normal when tested 2 months after delivery. Four of the 58 pre-eclamptic patients had raised blood urea during pregnancy but the values were normal during the puerperium, 2 months and 12 months after delivery. Six out of 13 eclamptic patients tested before delivery had raised blood urea values which were normal when examined in the puerperium. Two eclamptic patients not tested before delivery had raised blood urea in the puerperium, but tests 2 months after delivery gave normal results. Another patient whose blood urea was normal in the puerperium had a high blood urea a few weeks later. This patient did not return for any further investigation and this was the only instance of high blood urea in the total 333 tests on patients examined 2 months after delivery. Urea estimations made on the blood of 10 of the 12 chronic nephritic patients before delivery were above 40 mgm./100 c.c. in 2 instances, and between 30 and 40 mgm. in another 3 instances. Tests were obtained 8 days after delivery from 8 of these patients including 3 of those whose blood urea was high before delivery. In 2 of these patients the blood urea became normal after delivery but in the remaining patient the urea was not back to normal until 2 months after delivery. Another patient had a high blood urea in the puerperium after a normal test before delivery and the value was normal 2 months after delivery. Of the 12 tests 2 months after delivery there were only 2 instances of raised blood urea, one having had high blood urea before delivery and a test not having been obtained in the puerperium. In the other case a test was not obtained during pregnancy or the puerperium.

2. *Urea Concentration-Excretion Test.*

The urea concentration-excretion test has previously been shown to be a more sensitive means of detecting renal efficiency in toxaemias of pregnancy,[1] and the present series of tests con-

firms the earlier results. If the total excretion of urea, after a dose of 15 grams, is less than 4 grams in 3 hours, the test indicates renal inefficiency. If the total excretion exceeds 4 grams and the urinary volume exceeds 300 c.c. in 3 hours combined with poor concentrating power in the hourly specimens, the test is regarded as doubtful. In Table II the numbers of normal, doubtful and low tests are illustrated.

Among patients with mild albuminuria (A & B) and those in the miscellaneous group, 14 of the 36 tests obtained before delivery indicated renal inefficiency. The kidney appeared to be functioning normally in 5 of these patients by the 8th day after delivery, and in 8 who were not tested in the puerperium renal function was normal 2 months after delivery. Twelve months after delivery renal function was still poor in one patient. Six patients not tested before delivery showed renal damage in the puerperium and in all instances the kidney was functioning normally 2 months afterwards.

Kidney impairment was demonstrated in 61 of the 104 patients with persistent albuminuria, pre-eclampsia and eclampsia who were tested before delivery. Rapid recovery to normal function occurred in the puerperium in 19 instances and tests were normal in 25 more of these patients 2 months after delivery. In 6 patients the kidney damage was still present 2 months after delivery and further tests were not obtained. The kidney condition was difficult to determine in 8 patients who had doubtful tests 2 months after delivery, while in the remaining 3 instances in which tests were doubtful in the puerperium, the kidney was functioning poorly 2 months after delivery. Thirty-eight patients not tested during pregnancy showed evidence of poor renal function in the puerperium, but 33 had recovered normal function within 2 months. In 3 patients renal damage still existed 2 months after delivery, but recovery occurred within 12 months. Of 2 patients whose tests were doubtful 2 months post-partum, one was not tested again, and in the other the condition of the kidney was still doubtful at the end of 12 months.

The chronic nephritic group is a small but interesting one since 9 of the 10 patients tested before delivery had poor renal efficiency, while it was doubtful in the tenth patient. Poor function persisted in 6 patients in the puerperium and in 4 of these renal inefficiency persisted for 2 months after delivery. In the only patient tested 12 months after pregnancy the renal efficiency was still impaired at that time.

Seven of the 15 patients with hypertension had poor renal function tests before delivery, 2 had recovered by the 8th day, 3 not tested in the puerperium were normal after 2 months, and 2 in whom renal inefficiency persisted in the puerperium, were normal 2 months later. In the group of 15 patients suffering from an accidental haemorrhage, 8 had renal inefficiency in the puerperium which cleared up within 2 months. In one instance renal inefficiency did not develop until after the puerperium.

3. *Fowweather Urea Clearance Test.*

The results of the Fowweather urea clearance test[3] agreed closely with those of the urea concentration-excretion test in the estimation of renal efficiency 2 months and 12 months after delivery. The detailed results will not be discussed since the test has been used as a confirmatory one leading to greater certainty in assessing the condition of the kidney.

4. *Albumin in the Urine.*

All the patients investigated were classified into various toxaemias depending on the presence of albumin during the pregnancy for varying periods of time, and its association with other signs and symptoms. The urine became free from albumin rapidly in some patients and more slowly in others during the puerperium, and in some patients it persisted for months after delivery. The latter aspect is the one of particular interest in this discussion. Albumin was found in the urine of 106 of the 333 patients whose renal condition was investigated 2 months after delivery. In 66.5 per cent of the urines from these patients there was only a trace of albumin, 22.5 per cent contained 0.1 to 0.5 grams of albumin per litre, and in 11 per cent there was more than 0.5 grams per litre. The association of this persistent albuminuria with the more severe toxaemias is shown in Table III.

Eighty-one patients had tests at both 2 and 12 months after pregnancy, and 28 had albuminuria when tested at 2 months. In 10 of these patients albumin was still present at the end of 12 months. From Table IV it will be observed that the persistent albuminuria occurred chiefly after eclampsia and pre-eclampsia, but the amount of albumin present was small.

Evaluation of Renal Function Tests.

Blood urea was higher than normal in only 26 of the 921

specimens tested in this series of patients. Most of the abnormal values occurred before delivery and frequently dropped to the normal level early in the puerperium. Since urea in the blood is not increased until there is only about one-quarter of the total kidney substance functioning, and although high values are not numerous, the test indicates dangerous renal involvement in such cases, and is of great value in the severe toxaemias. Renal inefficiency was proved to exist in many patients by the demonstration of low results in 217 of the 921 urea concentration-excretion tests. Forty-eight per cent of the tests which were obtained during pregnancy showed kidney damage, as did 29 per cent of those in the puerperium, 7 per cent 2 months after delivery and 5 per cent 12 months after delivery. These figures clearly illustrate the effect of the toxaemias during pregnancy, the improvement in many patients immediately after delivery, and in most patients between the puerperium and 2 months after delivery. A small group of patients showed evidence of persistent renal damage 12 months after toxaemic pregnancy. In a few patients renal damage was not detected until after delivery.

Albuminuria seems to be the most delicate indication that the kidney is still abnormal since 31 per cent of the patients tested 2 months after delivery had at least traces of albumin in the urine while only 7 per cent had poor renal function tests at that time. Albuminuria persisted for at least 12 months in 10 out of 28 women who had positive tests for albumin 2 months after delivery.

These tests enable the response to treatment to be followed. Persistence or increase in the amount of albumin and poor renal function tests during pregnancy may indicate the necessity for the termination of pregnancy. In patients in whom pregnancy is allowed to continue, repetition of tests is important in detecting whether improvement, failure to respond to treatment, or actual deterioration of kidney function has occurred and so the real value of the treatment being given can be assessed. Poor renal function tests in the absence of clinical signs and symptoms may act as a warning of future serious developments. When tests after delivery show rapid recovery of the normal kidney function there is probability of a normal subsequent pregnancy. When albumin and renal inefficiency persist for as long as 12 months, more permanent renal damage is indicated, and such information is of great value when the question of a further pregnancy is involved.

B. The Urea Concentration-Excretion Test During and After Toxaemic Pregnancy.

It has been shown that the urea concentration-excretion test is a more sensitive means of estimating the efficiency of the kidney in pregnancy than other renal function tests[2] and some new facts in relation to this test before and after toxaemic pregnancy are now recorded. The percentage of patients excreting various amounts of urea per 3 hours after 15 grams of urea, in tests taken during pregnancy and 8 days, 2 months and 12 months after pregnancy, have been represented diagramatically for the various toxaemias of pregnancy (see diagram). A similar diagram has been constructed for the excretion of urea during normal pregnancy. Inspection of the diagram shows that there is a tendency for the amount of urea excreted per 3 hours to increase after delivery. In many patients the renal function improves to such an extent that patients with renal inefficiency during pregnancy have normal function in the puerperium. On the other hand some patients show improvement in urea excretion in the puerperium but the tests also show that some kidney damage still exists. A marked increase in the number of patients excreting less than 4 grams of urea per 3 hours is noted during pregnancy in the severe toxaemias when compared with the urea excretion of normal or mildly toxaemic patients.

The mean value for the urea excretion per 3 hours, calculated from the results of tests on 64 normal pregnant women, was 5.3 grams. The means of the values for total excretion of urea in toxaemic pregnancy, and 8 days, 2 months and 12 months after delivery, are correlated in Table V.

From this table it appears that there is a slight decrease in total urea excretion even in normal pregnancy. There is a slightly greater decrease in total urea excretion in the mild toxaemias (albuminuria A & B) and a marked decrease in the severe toxaemias—persistent albuminuria C, pre-eclampsia and eclampsia—during pregnancy. This decrease in urea excretion in the severe toxaemias was found to be highly significant, but that between mild toxaemias and normal patients during pregnancy was too small to be significant statistically. In post-partum tests the means were higher than those during pregnancy, except in the case of chronic nephritis, and a further increase occurred 2 months after delivery. The increases between ante- and post-partum tests in albuminuria C and pre-eclampsia were statistically significant but those between such tests in the groups

albuminuria A, B, and chronic nephritis were not. The increase in urea excretion 2 months after delivery when compared with that 8 days after delivery was highly significant in both mild and severe toxaemias, with the exception of chronic nephritis in which group insufficient data was available. A further increase was not found when urea excretion was estimated 12 months after delivery except in the eclamptic group in which the increase was statistically significant. The mean value for excretion of urea in the 3 hours, after a dose of 15 grams of urea, is about 6.5 grams in the normal woman. Normal pregnancy decreases the power of the kidney to excrete urea and the mean value was found to be 5.3 grams. The decrease was slightly greater in mild toxaemias (0.4 gms./3 hours), a marked decrease occurred in severe toxaemia (1.7—2.1 gms.), and it was most pronounced in the chronic nephritic group for which the mean excretion was 3.1 grams per 3 hours.

Urea excretion improves in all types of toxaemia immediately after delivery but the mean values, ranging from 5.1 gms. in albuminuria A to 3.5 gms. in chronic nephritis, are lower than those found at the end of 2 months after delivery when the range of mean values was 6.7 gms. in albuminuria A to 5.6 gms. in eclampsia. The mean values of urea excretion remain constant from 2 months to 12 months after pregnancy except in eclampsia. In this toxaemia there is an improvement in excretion from 8 days to 2 months post-partum and a further increase from 2 months to 12 months after delivery. It is evident, therefore, that the complete recovery of excretory power by the kidney following eclampsia is a slow process. The chronic nephritic patients were few in number and did not return for tests after delivery, hence, further information is not available.

C. Value of Renal Function Tests in the Puerperium.

It has been stated that renal function tests are of little value until about 6 weeks after delivery, since the conditions of diet and rest while in hospital are more favourable to normal results during the puerperium. Harris[4] states that the absence of signs of nephritis 3 weeks after delivery in no wise excludes the possibility of renal damage. Since less gross renal conditions are detected by the urea concentration-excretion test, the results of this test during pregnancy and at intervals of 8 days, 2 months and 12 months after delivery have been used to investigate these claims. Tests were obtained from 280 patients, but those from

55 patients were excluded because of difficulty in interpretation of some of the results. An analysis of urea concentration-excretion tests from 225 patients during the puerperium and at the end of 2 months is summarized in Table VI.

In only 1 per cent of the patients investigated did the renal efficiency show deterioration when examined 2 months after delivery. In another 5 per cent, in which the tests were difficult to interpret during the puerperium, the kidneys were inefficient 2 months after delivery, thus not more than 6 per cent of the tests showed kidney function to be worse 2 months after delivery than during the puerperium. In 56 per cent of the patients the kidney function did not show any variation in tests during the interval. Thirty-two per cent of the whole group had kidney involvement during the puerperium; they had recovered normal kidney function at the end of 2 months. Statistical analysis proved that a definite improvement in kidney function was shown when tests 8 days and 2 months after delivery were compared.

Table VII shows the results obtained by comparing tests from 67 patients 2 months and 12 months after delivery. In 94 per cent of the patients the tests were similar at both times, and 6 per cent who showed some kidney impairment 2 months after delivery had recovered normal kidney function 12 months after pregnancy. Renal dysfunction did not develop in a single patient in the interval between investigations.

Analysis of tests 2 months and 12 months after pregnancy did not show that any improvement or deterioration in renal function, which was significant statistically, had occurred in the interval between the tests.

The evidence presented does not support the contention that tests some time after toxaemic pregnancy are more likely to reveal renal inefficiency than those obtained during the puerperium. Definite deterioration was found in only 1 per cent of the patients studied and possible deterioration in another 5 per cent, whereas tests agreed in 62 per cent, and improvement occurred in 32 per cent in the interval from 8 days to 2 months after delivery. That this improvement was a permanent effect so long as the patient did not again become pregnant was shown by the fact that deterioration in renal function did not occur in any case in the interval between 2 months and 12 months after delivery. Tests 2 months after delivery are very useful in picking out those patients whose kidney damage is recovering very

slowly and those with permanent involvement. A further elimination of those with slowly recovering normal function is obtained by testing patients 12 months after delivery.

Summary

The blood urea test is useful in indicating gross renal damage resulting from severe toxaemias of pregnancy or milder toxaemias in association with chronic nephritis, during the pregnancy.

The urea concentration-excretion test is a much more sensitive test than the blood urea test and enables less gross renal damage to be detected during a toxaemic pregnancy. It can also be used to trace the rate of recovery of renal efficiency or prove the presence of permanent damage by observation of the results of tests at intervals for some months after delivery.

The presence of albumin in the urine of a large number of patients whose kidneys had recovered normal function in relation to excretion of urea in tests 2 months after pregnancy, and the persistence of traces of albumin in the urine of many of these patients even 12 months after delivery show that this is an even more delicate means of indicating that the kidney is not completely normal.

These renal function tests are of great value in the treatment of the current toxaemia and if investigations are carried on over a period of months after the initial toxaemia, give information useful in the management of subsequent pregnancies.

A study of the urea concentration-excretion test during and after pregnancy shows that the excretion of urea by the kidney is decreased slightly even by normal pregnancy, but that a marked diminution in renal efficiency frequently occurs in severe toxaemias during the pregnancy. The recovery of normal function takes place often within 8 days and usually within 2 months of delivery, by which time maximum urea excretion is attained. In eclampsia the recovery is slower, the maximum excretory power being regained within 12 months.

The contention that renal inefficiency could be detected in a greater number of patients some time after delivery rather than during the puerperium was disproved. Renal function did not alter in the interval 8 days and 12 months after delivery in two-thirds of the patients investigated, and it improved during this period in practically all of the remaining patients. Deterioration in renal function 2 months after delivery was very rare.

ACKNOWLEDGEMENT

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TABLE I.

Type of toxaemia	Blood urea test				Urea concentration-excretion test				Fowweather urea clearance				Total tests
	No. of tests				No. of tests				No. of tests				
	A. P.	8 days	2 mos.	12 mos.	A. P.	8 days	2 mos.	12 mos.	A. P.	8 days	2 mos.	12 mos.	
Albuminuria A	10	16	24	7	11	17	25	7	8	10	24	7	166
Albuminuria B	14	31	39	9	13	31	39	9	7	27	39	9	267
Albuminuria C	47	51	55	15	46	50	55	15	32	36	51	15	468
Pre-eclampsia	58	69	84	20	57	67	84	20	40	47	84	17	647
Eclampsia	15	65	53	23	9	67	54	23	5	38	41	22	415
Chronic nephritis	17	11	13	1	17	11	12	1	9	6	10	1	109
Hypertension	19	10	15	—	19	10	15	—	18	10	15	—	131
Accidental haemorrhage ...	3	16	17	6	3	15	17	6	3	12	15	6	119
Miscellaneous	14	25	33	16	14	23	33	17	10	18	32	17	252
Total	197	294	333	97	189	291	334	98	132	204	311	94	2,574

TABLE II.

SHOWING THE NUMBERS OF NORMAL, DOUBTFUL, AND LOW UREA CONCENTRATION-EXCRETION TESTS DURING AND AFTER DIFFERENT TYPES OF TOXAEMIC PREGNANCY.

	UREA CONCENTRATION-EXCRETION TESTS											
	Ante-partum			Post-partum			2 months			12 months		
	Normal	?	Low	Normal	?	Low	Normal	?	Low	Normal	?	Low
Albuminuria A	8	—	2	10	4	2	23	1	—	7	—	—
Albuminuria B	5	2	5	19	6	5	35	3	—	8	—	1
Albuminuria C	18	4	24	22	7	20	46	5	4	14	2	1
Pre-eclampsia	24	4	31	38	12	24	71	6	7	18	—	1
Eclampsia	3	—	6	27	11	25	43	4	6	22	1	1
Chronic nephritis ...	—	1	9	—	3	6	5	1	4	—	—	1
Hypertension	7	1	7	5	—	5	14	1	—	1	—	—
Accidental haemorrhage ...	3	—	—	11	1	3	15	—	1	6	—	—
Miscellaneous	6	1	7	13	1	8	31	1	1	15	—	—

TABLE III.

CORRELATION OF PERSISTENCE OF ALBUMIN IN PATIENTS TESTED 8 DAYS AND 2 MONTHS AFTER TOXAEMIC PREGNANCY.

Type of toxaemia	No. of patients with tests at 2 months	No. of patients with albumin at 2 months	Albumin		
			No. with trace	No. with 0.1 to 0.5 grams	No. with more than 0.5 grams
Albuminuria A	24	2	2	—	—
Albuminuria B	39	8	7	1	—
Albuminuria C	55	18	15	1	2
Pre-eclampsia	84	44	28	11	5
Eclampsia	53	16	7	6	3
Chronic nephritis	13	6	4	1	1 (gross)
Hypertension	15	4	3	—	1 (gross)
Accidental haemorrhage	17	6	4	2	—
Miscellaneous	33	2	—	2	—
Total	333	106	70	24	12

TABLE IV.

CORRELATION OF PERSISTENCE OF ALBUMIN IN PATIENTS TESTED 2 AND 12 MONTHS AFTER TOXAEMIC PREGNANCY.

Type of toxaemia	No. of patients at 2 and 12 months	Albumin				Albumin			
		No. with albumin at 2 months	No. with trace	No. with 0.1 to 0.5 grams	No. with more than 0.5 grams	No. with albumin at 12 months	No. with trace	No. with 0.1 to 0.5 grams	No. with more than 0.5 grams
Normal	–	–	–	–	–	–	–	–	–
Albuminuria A	7	–	–	–	–	–	–	–	–
Albuminuria B	9	5	5	–	–	–	–	–	–
Albuminuria C	12	6	4	–	2	1	1	–	–
Pre-eclampsia ...	18	8	3	4	1	5	3	1	1
Eclampsia	14	6	4	2	–	3	3	–	–
Chronic nephritis ...	1	–	–	–	1	–	–	–	1
Hypertension ...	1	–	–	–	–	–	–	–	–
Accidental haemorrhage	6	3	3	–	–	–	–	–	–
Miscellaneous ...	13	–	1	–	–	1	–	1	–
Total	81	28	20	6	4	10	7	2	1

TABLE V.

SHOWING THE MEAN TOTAL EXCRETION OF UREA PER 3 HOURS IN THE VARIOUS TOXAEMIAS OF PREGNANCY.

Type of toxaemia	Mean total excretion of urea per 3 hours (mean value for normal pregnancy 5.3 grams)			
	Ante-partum	Post-partum	2 months post delivery	12 months post delivery
Albuminuria A	4.9	5.1	6.7	6.7
Albuminuria B	4.8	4.9	6.1	—
Albuminuria C	3.5	4.5	6.4	6.5
Pre-eclampsia	3.6	4.4	6.2	6.3
Eclampsia	—	4.4	5.6	6.7
Chronic nephritis ...	3.1	3.5	—	—

TABLE VI.

CORRELATING UREA CONCENTRATION-EXCRETION TESTS SHOWING KIDNEY EFFICIENCY OR INEFFICIENCY 8 DAYS AND 2 MONTHS AFTER DELIVERY.

Group	Tests in the puerperium	Tests 2 months after delivery	Number of patients	Patients, per cent
1	Normal function	Normal function	125	56.0
2	Renal inefficiency	Renal inefficiency	14	6.0
3	Renal inefficiency	Normal function	73	32.0
4	Normal function	Renal inefficiency	2	1.0
5	Doubtful	Renal inefficiency	11	5.0
	Total patients in these 5 groups		225	100

TABLE VII.

CORRELATING UREA CONCENTRATION-EXCRETION TESTS SHOWING KIDNEY EFFICIENCY 2 MONTHS AND 12 MONTHS AFTER PREGNANCY.

Group	Tests 2 months after delivery	Tests 12 months after delivery	Number of patients	Patients, per cent
1	Normal function	Normal function	62	92.5
2	Renal inefficiency	Renal inefficiency	1	1.5
3	Renal inefficiency	Normal function	4	6.0
4	Normal function	Renal inefficiency	–	—
	Total number of patients in these 4 groups		67	100.0

The Differential Diagnosis of Vaginitis in Menopausal Women

BY

HUGH C. MCLAREN, M.D. (Glas.), F.R.F.P.S. (Glas.), M.R.C.O.G.

THE cessation of menstruation is followed by physiological changes in the vaginal epithelium which may present a clinical appearance closely resembling vaginitis. A preliminary article is presented on the diagnosis of vaginitis and especially to differentiate normal menopausal appearances from pathological conditions.

SPECIAL AETIOLOGICAL FACTORS

In sexually mature women, unlike those in the menopause, oestrin deficiency cannot be postulated as a predisposing cause of vaginitis. It appears that the amount of oestrin necessary to produce menstruation is greatly in excess of that required for the maintenance of healthy vaginal epithelium. This fact is well illustrated in treating certain types of amenorrhoea in which gross atrophy of the vaginal epithelium exists. Minute doses of follicular hormone will result in great hypertrophy of the vaginal mucosa. Much larger doses are required to produce corresponding changes in the endometrium. Moreover, in histological sections of vaginitis in the sexually mature woman the affected tissue shows areas of desquamation alternating with areas of apparently normal epithelium. If gross oestrin deficiency were present one would expect to find generalized thinning of the epithelium with loss of its normal differentiation with cell layers.

In some post-menopausal women the vaginal epithelium may show evidence of oestrin deficiency, although the majority of women retain normal vaginal mucosa. It is reasonable to assume, therefore, that in the group in which thinning occurs, added trauma to an atrophic mucosa may permit the entry of infecting organisms. The effect of such trauma is evident on passing a speculum when small pin-point haemorrhage from the mucosa can be observed. Coitus might cause similar damage. In the study of over 200 cases, we were surprised at the number of patients who continued to have coitus for years after the

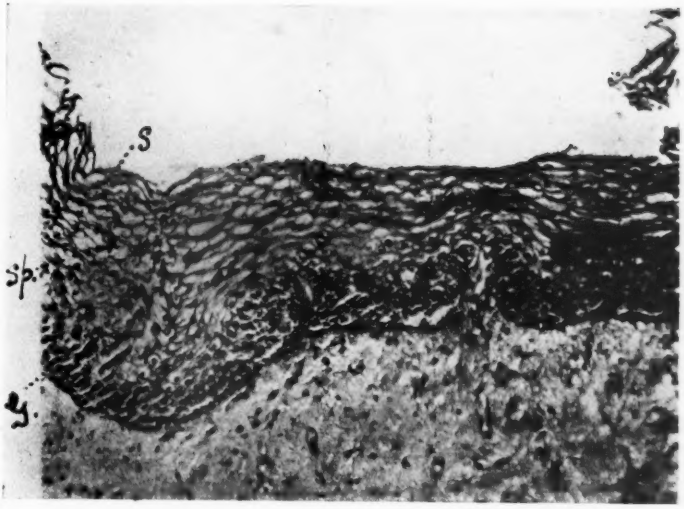

FIG. 1

Mrs. C., aged 88. No discharge: atrophic labia minora, entrance to vagina smooth and shining. Vaginal mucosa appeared spotted with red areas. No rugosae. Upper vagina very narrow, cervix small.

The vaginal epithelium shows only traces of the superficial flat layers (*S*). The stratum spinosum (*sp*) and basal layers (stratum germinativum) (*G*) are clearly seen. Glycogen was abundant in a section stained by Best's method.

M. Average thickness 200 μ (H. & E.) $\times$ 136

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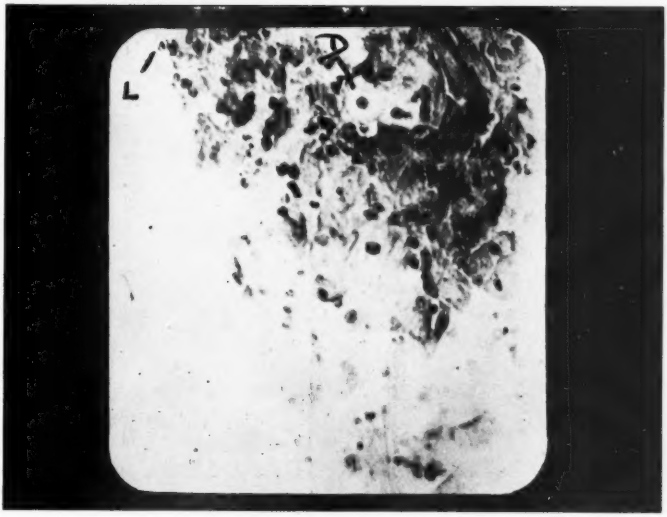

FIG. 2

Mrs. D. Vaginal smear shows deep cells (*D*) of the stratum spinosum layer and leucocytes (*L*). Classified as Grade II.

Papinicolau's stain × 224

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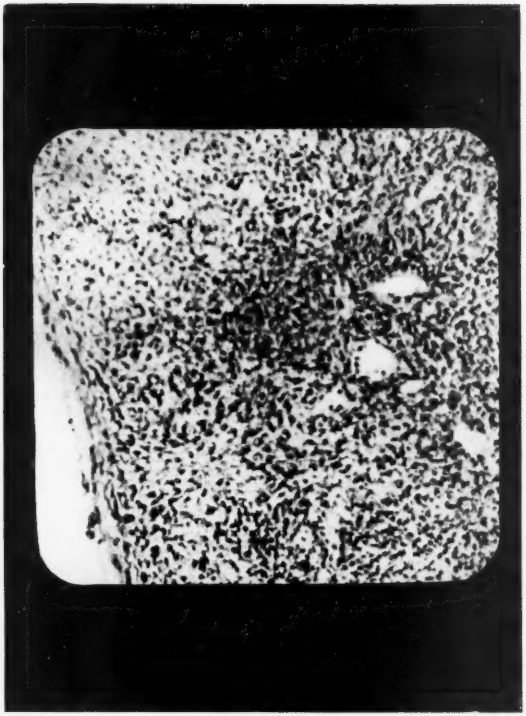

FIG. 3

VAGINAL BIOPSY FROM CASE SHOWN IN FIG. 2

Complete desquamation of this area of epithelium. Intense infiltration of submucosa with round cells and leucocytes. Note dilated blood-vessels.

Best's stain × 146

M.

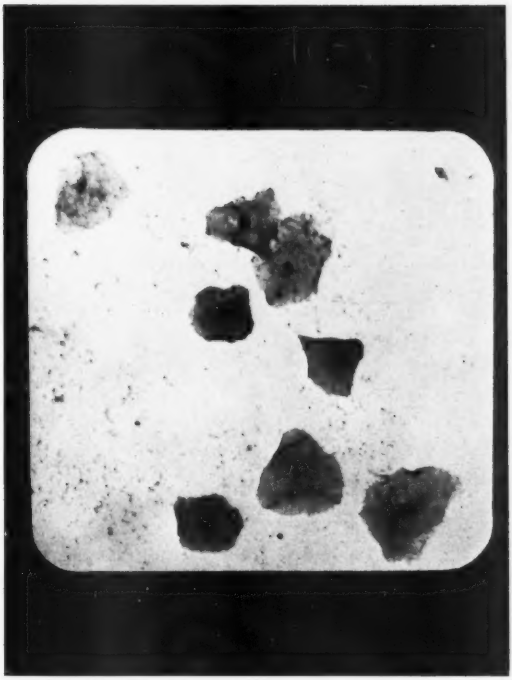

FIG. 4—AFTER 28 MGM. STILBOESTROL
Grade III. Smear: flat squames and *b*. Döderlein predominated.

FIG. 4*a*—AFTER 28 MGM. OF STILBOESTROL
3-layered normal epithelium. (*S*) Superficial flat layer; (*Sp*) stratum spinosum with much glycogen (black in photograph); (*G*) stratum germinativum. The submucosa is almost free from round cells. Best's stain × 60

M.

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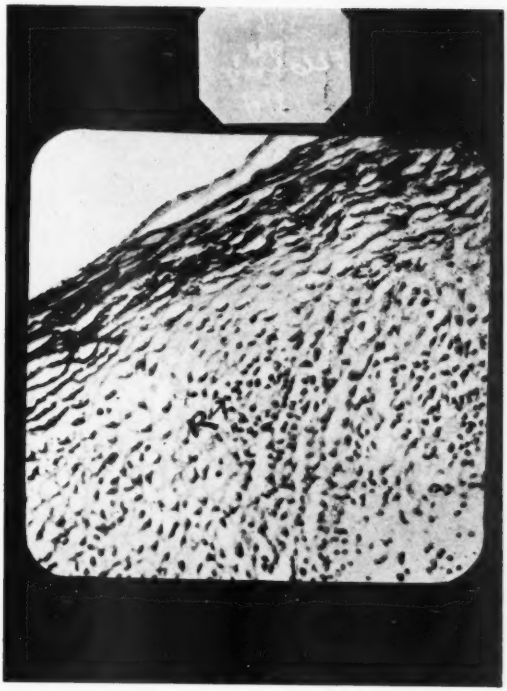

FIG. 5

Mrs. G. (2), aged 52. Uterus and 2 ovaries removed 18 months ago.

No discharge; the mucosa looked pale and smooth. Epithelium senile but differentiated to some extent and showing glycogen (black). Round cells (*R*) surrounding dilated blood-vessels in submucosa.

Average thickness 90μ.

M. Best's stain × 215

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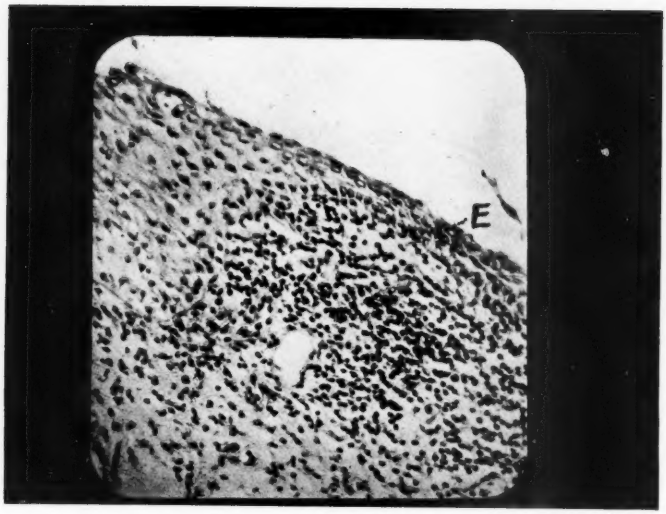

FIG. 6

Miss M. Normal case, aged 12. No leucorrhoea. Vaginal mucosa lined by 2 layers of small globular epithelial cells (*E*). In the submucosa dilated blood-vessels and marked round cell infiltration are evident.

Best's stain × 94

menopause. For example, one patient had sexual intercourse regularly at the age of 78.

The common infecting agent in vaginitis in sexually mature women has been the subject of much research in past years. Non-haemolytic streptococci,[1] fungi[2] and trichomonas vaginalis[3] have been suggested, but doubt still exists on this point. Little is known about the causal organisms of post-menopausal vaginitis, but it seems probable that similar types are responsible.

The diagnosis of vaginitis rests on four findings:

1. Discharge from the vagina.
2. The clinical appearance of the vagina.
3. Examination of the vaginal contents.
4. Histological evidence from a mucosal biopsy.

1. *Vaginal Discharge.*

An offensive yellow discharge is the usual symptom which compels the patient to seek advice. A multiparous woman is commonly less sensitive to leucorrhoea than a nullipara and it is often difficult to make an accurate estimate of the amount of the discharge before a pelvic examination has been done. Information regarding the number of vulval pads the patient requires may provide a rough gauge of the amount of discharge.

2. *Clinical Appearances.*

Before making a clinical diagnosis of post-menopausal vaginitis a knowledge of the varied appearances of the vaginal mucosa following the menopause is essential. Speculum examination of the vaginal wall of a post-menopausal woman may show appearances indistinguishable from those of a sexually mature woman. In some cases, however, the appearance of the mucosa may closely simulate vaginitis and lead to a wrong diagnosis. In a study of 58 women who had passed spontaneously into the menopause we found that 29 (58 per cent) had clinically abnormal vaginal mucosa. In 14 cases the mucosa was smooth and pale without rugosae, and in 15 cases it was smooth and studded with red areas. The latter group closely resembled true vaginitis but histological study failed to confirm it.

The 15 patients with red spotted mucosa did not have excessive discharge.

Histological study of the mucosa in 5 cases was possible. The findings are tabulated overleaf.

CASES WITH RED SPOTTED MUCOSA

No.	Age	Discharge	Vaginal smears *p*H	Cell-smears	Bacteria	Mucosal biopsy
1	53	Nil	?	III* (Normal)	*b.* Döderlein only	Normal: 3 layered average thickness 250μ Glycogen +
2	65	Nil	6.5	II	Scanty cocci	Normal: 3 layered average thickness 200μ Glycogen +
3	73	Nil	?	?		Normal: 3 layered average thickness 250 μ Glycogen
4	75	Nil	7.2	III	Mixed organisms	Normal: 2 layered average thickness 200 μ Glycogen
5	88	Nil	6.2	III	Almost pure *b.* Döderlein	Normal: 3 layered average thickness 200 μ Glycogen (See Fig. 1.)

* Grade III cell-smears usually come from normal mucosa.[1]

Case No. 5 is reproduced as an example.

In 15 cases (26 per cent), therefore, of a series of normal post-menopausal women the appearances of the vagina were similar to that seen in vaginitis. The absence of discharge, the examination of the vaginal contents and (in 5 of the cases) the histological examination of the mucosa confirmed the fact that none of these was a true case of vaginitis. Nevertheless, it is common to encounter cases in which doubt exists. In such cases a small biopsy will be of value. Working from a knowledge of the histological variations which occur normally in the menopausal vagina, the pathologist will have little difficulty in diagnosing true vaginitis. (Vide p. 747.)

3. *Examination of Vaginal Contents.*

The amount of secretion from the vagina is difficult to estimate from the vague information gathered from the patient. In the menopause, the amount of secretion in the vagina normally becomes very scanty. It consists mainly of cervical mucus, which, moreover, is diminished in amount as compared to the sexually mature woman. Evidence of abundant muco-

purulent discharge is, therefore, important in the diagnosis of vaginitis, and a rough quantitative estimate can be made on pelvic examination.

Detailed investigation of the vaginal secretion usually consists of the following: *p*H estimation, wet-drop, cell-smear, bacteriological and histological examinations.

(*a*) *pH Estimation.* Quite apart from vaginitis the secretion of the vagina tends to become alkaline in the menopause, although occasionally readings of 5 or less may be obtained. *p*H values, therefore, are seldom of significance in the diagnosis of vaginitis. They afford, however, an easy clinical method of estimating the success or failure of treatment of post-menopausal vaginitis with follicular hormone. A simple method is sufficiently accurate, e.g. with the British Drug Houses Colorimeter. In successfully treated cases the *p*H value rapidly falls to 5 or less and the other confirmatory clinical and laboratory findings invariably bear out this evidence of improvement in the vaginal mucosa.

(*b*) *Wet-Drop Examination.* This method is useful for discovering trichomonas vaginalis which can readily be found in a warm saline mixture of fresh secretion.

It must be observed that trichomonas and leucocytes are frequently found in the vagina from vaginitis. For instance, we found pus and trichomonas in 26 out of 278 specimens (9 per cent) obtained from women who had reached the menopause (spontaneously or by artificial induction). Analysis brought out the following points:

1. Leucorrhoea was slight in 5 (19 per cent), absent in 12 (46 per cent) and doubtful in 9 (35 per cent).

2. The vagina appeared normal in 16 cases (62.6 per cent), red in 7 (27 per cent), and in 3 (11 per cent) examination was unsatisfactory.

3. (*a*) Histological examination of 17 specimens gave normal findings in 14 (82 per cent), the remaining 3 showed the following: moderate, senile thinning (1), acute vaginitis (1) and subacute vaginitis (1).

(*b*) Mucosal biopsies of 5 out of 7 cases with red mucosa (akin to vaginitis) were examined. Four were normal, 1 showed subacute vaginitis.

It is obvious, therefore, that pus and trichomonas in the vagina is insufficient evidence for a diagnosis of vaginitis. Even if the mucosa producing the secretion appears red, a biopsy may not show evidence of inflammation. These findings are in agree-

ment with Mohr.[4] He examined 212 healthy sexually mature women and in 52.6 per cent found trichomonas in vaginal smears.

(*c*) *Vaginal Cell-Smears*. Vaginal smears are of little use in the diagnosis of vaginitis. In a previous study[5] we correlated a large number of cell-smears with histological specimens of the underlying epithelium. We concluded that the superficial cells from the vagina gave a very inaccurate gauge of the type, thickness and health of the underlying mucosa. For instance, many cell-smears from vaginitis were indistinguishable from those obtained in healthy post-menopausal women. Certain smears, however, were of value in forecasting normal epithelium. These included flat squames, average diameter of which was over 45 μ, and perhaps some leucocytes. Such smears agreed with the underlying normal epithelium in 90 per cent of cases. A vaginal wall subject to inflammatory changes is unlikely to yield smears of this type. This fact is of some value in the excluding vaginitis in a suspected case. Similarly, a cell-smear is roughly an accurate index of the cure of vaginitis. The reappearance of large flat squames with loss of excessive pus cells points to the recovery of the vaginal wall. (Fig. 4.)

(*d*) *Bacteriological Investigation*. In assessing the value of bacteriological findings in vaginitis it is necessary to have a knowledge of the great variations normally found in the vagina following cessation of menstruation. In general, the organisms tend to become mixed and the *b*. Döderlein less predominant. In 60 consecutive smears from women who had spontaneously reached the menopause the following results were obtained:

Predominance of *b*. Döderlein ...	17 (28.3 per cent).
Mixed Organisms	32 (53.3 per cent).
Scanty Gm. positive ± cocci (only)	11 (18.3 per cent).

In practice, a smear showing mainly *b*. Döderlein suggests a healthy vaginal wall and histological investigation invariably confirms this. The presence of mixed organisms (which might be taken as a variation from normal in a sexually mature woman) may not be abnormal for a post-menopausal woman. Certainly the finding cannot be used even as a confirmatory fact in the diagnosis of vaginitis.

(*e*) *Vaginal Biopsy*. To avoid ambiguity in the diagnosis of vaginitis it is our practice to remove a small area of vaginal wall

for histological study. A Cusco's speculum is inserted and the blades are separated to press back the lateral vaginal walls. It is a simple and almost painless procedure to raise an area of posterior wall with a toothed forceps and, using a new blade in a Bard-Parker scalpel, to shave off $\frac{1}{4}$ inch of tissue. Bleeding is seldom troublesome and is easily controlled by a small vaginal pad.

The microscopic appearances in acute post-menopausal vaginitis are fairly typical (Fig. 3). Patchy superficial desquamation of the epithelium is present. Intervening areas of apparently normal tissue with abundant glycogen may be seen. The desquamation of epithelial cells exposes small areas of the submucosa which are the site of intense infiltration by lymphocytes and possibly plasma-cells. The submucosal blood-vessels are dilated and leucocytes can be seen passing through their walls. The particulars are as follows:

Mrs. D., aged 48, widow, para 4. Radium menopause 2 years ago. Complained of profuse green vaginal discharge which required frequent changes of underclothes and caused much vulvar itching. The vulva appeared red and excoriated. The vagina was dull red in appearance and tender, there being numerous small red areas studded over the wall, giving it a mottled appearance. Much pus was present. The cervix was not ulcerated, but was red and spotted over the portion. Smears of urethra and cervix were taken to exclude gonorrhoea. The vaginal secretion showed pus and trichomonas and its *p*H was 6.8. Gram's stain showed a mixture of organisms, mostly *b.* coli.

Local treatment was not given, but 1 mgm. stilboestrol was given for 28 days and the normal appearances were obtained, both clinically and histologically. (Figs. 4 and 4*a*.)

In this case the diagnosis of the vaginitis was easy. There are, however, cases in which doubt exists at clinical examination and in which a mucosal biopsy is essential for an accurate diagnosis. Even the histological diagnosis of vaginitis may prove difficult unless the histologist is familiar with the physiological changes which may occur in the vagina in the menopause. In 7 out of 142 biopsies from women who had the menopause induced surgically or by radium, we observed histological changes closely resembling those of vaginitis, viz. thinning of the vaginal epithelium and infiltration of the submucosa by round cells.

CASES WITH SUB-EPITHELIAL INFILTRATION

	Type of menopause	Leucorrhoea	Appearance of vaginal mucosa	Epithelium (thickness)	Round cell infiltration
1	Hysterectomy +1 ovary	Nil	Red	Normal 192 μ	+
2	Hysterectomy +2 ovaries	Nil	Pale, smooth	Senile 90 μ	+
3	Hysterectomy +2 ovaries	?	Normal, but peels easily	Mod. senile 156 μ	+
4	Hysterectomy +2 ovaries	Yellow	Red + +. Bled with ease	Normal 420 μ	+ +
5	Hysterectomy +2 ovaries	Nil	Normal	Mod. senile 167 μ	+
6	Ra menopause	Nil	Normal	Senile 89 μ	+
7	Ra menopause	Nil	Pale, smooth	Mod. senile 115 μ	+

The biopsy from case No. 2 is reproduced. It demonstrates the points which make normal menopausal epithelium resemble vaginitis. (Fig. 5.)

Round cell infiltration of the submucosa suggests that the latter has been invaded by bacteria resulting in an inflammatory reaction. It appears, however, that this is not invariably the case as, for example, in the vagina before the *ménarche* (Fig. 6).

There is presumably a lack of follicular hormone in both cases. This may be responsible for the presence of lymphocytes in the submucosa.

It is the opinion of Maximov,[6] and of Smith and Brunner,[7] that in sexually mature women the accumulation of round cells in the submucosa is a physiological feature. Smith and Brunner define 5 degrees of infiltration of which the first 3 are within physiological limits. Our own experience in healthy sexually mature and menopausal women is that, if one neglects a few scattered lymphocytes, round cell infiltration of the submucosa is a rare occurrence. In the above cases (with the possible exception of Case 4), it would seem that the accumulation of lymphocytes in the submucosa may be a physiological occurrence. It seems certain that their presence is not part of an inflammatory reaction.

The differential diagnosis of post-menopausal vaginitis, therefore, is made difficult by the fact that, in the normal menopausal vagina, thinning of the mucosa and sub-epithelial infil-

tration produce appearances closely resembling true vaginitis. Nevertheless, with these difficulties in mind, we advocate the use of mucosal biopsies for the accurate diagnosis of post-menopausal vaginitis.

Conclusions

A preliminary article is presented on the diagnosis of post-menopausal vaginitis. The difficulty in diagnosing true inflammation of the vagina in the menopause is emphasized. Reliance on one method of investigation, whether clinical or laboratory, may lead to a mistaken diagnosis. It is suggested that the only certain method of diagnosis consists of clinical and histological examination of the vaginal mucosa. In histological examination, *p*H estimations, bacteriological and cell-smear examinations, a clear knowledge of the physiological variations of each is essential as a background for the diagnosis of vaginitis.

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Meigs' Syndrome (Ovarian Fibroma with Ascites and Hydrothorax): Report of a Case

BY

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THE syndrome of ascites and hydrothorax in association with fibroma of the ovary has been fully described recently in America. In 1937, J. V. Meigs and Cass[1] collected and reported 7 cases: in the same year Rhoads and Terrell[2] reported one case. Two cases were reported by Weld in 1938.[3] As far as I can ascertain, there have been only 15 cases of this rare syndrome reported in the world's literature. Although Meigs' syndrome is undoubtedly uncommon, probably it is not quite so rare as it seems; there is little doubt that often it is missed. The important aspect of the question is that removal of the fibroma is curative. From the physician's point of view, a knowledge of the syndrome is of value, as otherwise it may happen that the case is repeatedly aspirated without any lasting benefit. A case came under my care in 1939: a diagnosis of Meigs' syndrome was made. The patient was being handed to the gynaecologists for operation when she collapsed rather suddenly. The post-mortem examination confirmed the clinical diagnosis.

CASE REPORT

M.A.G., aged 44, a married lady, was admitted to Grove Road Hospital, Richmond, on the 22nd July, 1939, with a history of lower abdominal pain for 6 months and increasing shortness of breath for the last 3 weeks. During the latter period the patient consulted her private doctor and he noticed the increase in the size of the abdomen. The patient had had 7 normal deliveries in the past, and had amenorrhoea for the last 12 months. There was nothing else of importance in the past history.

On examination, the patient was rather pale and extremely breathless. The temperature was 97.4°F., the pulse-rate 112, and

FIG. 1.

Uterus and adnexa, showing the bilateral ovarian fibroma.

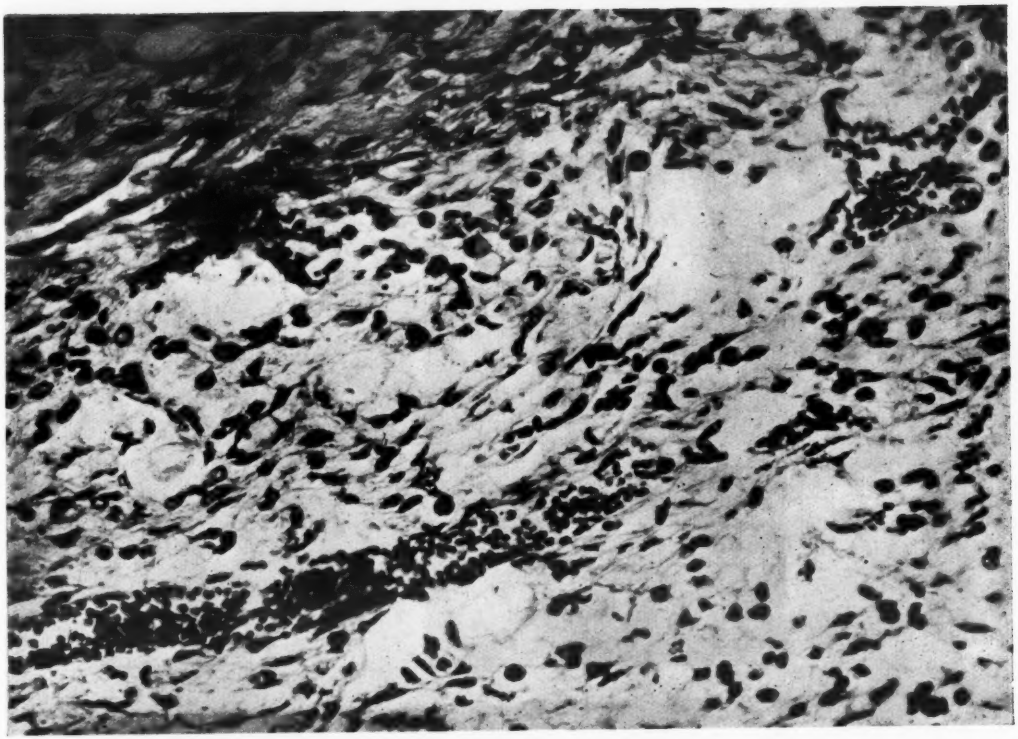

FIG. 2.
Micro-photograph of section from ovarian fibroma.
Magnification × 400

the respiration-rate 36. There was no emaciation, but she looked exhausted.

The apex-beat was displaced to ½-in. outside the papillary line. Over the right side of the chest there was little movement with respiration, the tactile fremitus was markedly diminished all over, and there was stony dullness with diminished air-entry over the entire area. There was increased air-entry over the left chest. The abdomen was moderately distended and contained a fair amount of free fluid. Palpation of the abdomen before paracentesis suggested the presence of a hard mass in the umbilical area. There was not any oedema of the legs. The central nervous system and the urine were normal.

Immediately after admission, the right chest was aspirated, over 3½ pints of clear, pale greenish liquid being withdrawn A considerable amount of liquid was left inside the pleural cavity. The pathological report on the pleural fluid was:—

"A straw-coloured fluid without any clot. Cells are numerous, almost entirely lymphocytes with some endothelial cells and a number of red cells. Tubercle bacilli not found. Culture—no growth."

On the 24th July, paracentesis abdominis was performed, 6½ pints of clear, straw-coloured liquid being removed. The report on the ascitic fluid was as follows:—

"This is a straw-coloured fluid which does not clot. Cells are not numerous and are mainly lymphocytes with some endothelial cells and red corpuscles. Tubercle bacilli not found. Culture—no growth."

Palpation of the abdomen after paracentesis revealed the presence of a very hard mass, slightly mobile, and tender on palpation, lying in the hypogastric region. Vaginal examination did not reveal anything abnormal except some tenderness in the left fornix.

On the 28th July, paracentesis of the right chest was repeated, 2 pints, 14 ounces of somewhat opaque, straw-coloured liquid being withdrawn. On the 4th August, 1939, the patient suddenly complained of faintness and, in spite of treatment, died in a little over an hour.

Post-mortem Findings

The following were the positive findings at the post-mortem:

There was a massive hydrothorax on the right side and a small one on the left.

The lungs were very small and collapsed, especially the right one. There was a fair degree of ascites. Nothing abnormal was found in the stomach or colon. Lying entirely above the pelvis towards the midline of the abdomen was a huge fibroma of the right ovary: there was a smaller ovarian fibroma on the left side. The general shape of the ovary was pretty much preserved in both tumours. The right one measured $14 \times 9.5 \times 8$ cm. Its surface was smooth, glistening and contained large, smooth lobes, intersected by shallow sulci. The tumour was very hard and on section the colour was dull white. The left ovarian tumour had identical characters, apart from its smaller size, the measurements being $9 \times 5 \times 5.5$ cm. Histological examination of both ovaries revealed the typical appearances of an ovarian fibroma. It may be of interest to point out that the azygos vein was of wide calibre, being twice as wide as the abdominal aorta: whether this is a coincidence or is related to the hydrothorax remains to be seen. At the moment the aetiology of the hydrothorax is hidden in complete obscurity. The sudden death of the patient is difficult of explanation, but may possibly have been due, partly at least, to shifting of, and pressure on, mediastinal structures by the massive right-sided hydrothorax.

My thanks are due to Dr. J. Ferguson, County Medical Officer, Surrey County Council, for permission to publish this case, and to Dr. J. Bamforth for the histological report.

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An Unusual Case of Carcinoma of the Cervix

BY

STANLEY WAY, M.R.C.S. (Eng.), L.R.C.P. (Lond.), M.R.C.O.G.

AND

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From the Departments of Gynaecology and Pathology, the Medical School, King's College, Newcastle-on-Tyne

THE following case seemed to us of sufficient rarity to warrant the publication of a short note.

The patient was a woman aged 56, and was admitted to the gynaecological ward of the Royal Victoria Infirmary, Newcastle-on-Tyne, on the evening of New Year's Day 1941, with a diagnosis of twisted ovarian cyst. She had had 8 children, her last pregnancy being in 1920. The menopause had occurred in 1930 at the age of 46. She had not previously been ill. On the night of 31st December she had been suddenly seized with violent abdominal pain which had caused her to fall on the floor. Almost immediately she began to vomit copiously and this continued up to, and after, her admission to hospital. The next day the pain was slightly easier but was now referred to the shoulder tip. On this day also, there was a slight vaginal haemorrhage, which was the first bleeding she had had since the menopause.

On examination she appeared gravely ill. Pulse-rate 120, volume feeble. Temperature 99.2° F. The abdomen showed board-like rigidity everywhere and extreme tenderness. Shoulder-tip pain was present. There was dullness in both flanks and shifting dullness. She was hiccoughing violently between bouts of vomiting, and her breath smelt strongly of acetone. On vaginal examination there was extreme tenderness, and the cervix was the seat of a carcinomatous ulcer which was involving the vault of the vagina in all quadrants.

She was seen an hour after admission by one of us (S.W.) who made a diagnosis of peritonitis due to ruptured pyometra due to carcinoma of the cervix, with terminal uraemia. As the patient appeared moribund there seemed no indication to do anything beyond easing her last hours of life. She was, therefore, given morphia grain $\frac{1}{2}$, and blood was taken for a blood urea esti-

mation. This proved to be 96 mgs. / 100 c.c. of blood. At 5 a.m. on the 2nd January she went into a coma; at 8.30 the pulse was hardly palpable and she died at 11 a.m., 12 hours after admission.

On 3rd January an autopsy was performed by one of us (J.S.) and the findings were as follows:

The peritoneal cavity was filled with green plastic exudate, causing loose adhesions between congested loops of bowel. In the pelvis were at least 500 c.c. of serous yellow pus. The uterus was enlarged and softened and on its anterior surface just below the fundus was a hole measuring 3.0 × 2.0 cms. This was found to lead directly to the uterine cavity. The latter contained a pyometra filled with foul greenish-yellow pus. The cervix was replaced by a hard craggy ulcer with a blackened sloughing base and raised friable edges. This ulcer had extended downwards to involve the upper third of the vagina, and the bases of the broad ligaments were hard and indurated. There was no relation between this ulcer and the hole previously referred to. The right and left iliac and para-aortic glands were enlarged and firm; on section they consisted of white neoplastic material. The bladder showed a moderate degree of basal cystitis and the kidneys, renal pelves, and ureters were normal. Examination of the other abdominal viscera did not reveal any abnormality, except the gall-bladder, which was chronically inflamed and contained some small stones. There were no signs of acute cholecystitis. The thorax and neck did not show any abnormality. The brain was not examined. Microscopical section of the cervical growth showed it to be a squamous-celled carcinoma. Section of the glands showed that they were infiltrated with growth. Unfortunately a biopsy was not taken of the edges of the hole through which the pyometra was escaping into the abdominal cavity, but macroscopically there was nothing to suggest that it was in any way connected with the growth. Nothing whatever was done either before or after admission which could have produced this rupture, and the only thing in her past history which might have produced any weakening of the uterine wall was the fact that she had had 8 pregnancies.

Summary

(*a*) A case of carcinoma of the cervix with peritonitis due to ruptured pyometra is described.

(*b*) Symptoms of the disease did not present themselves until the rupture of the pyometra, which led to death.

(*c*) An accurate diagnosis was made before death on the typical signs of a ruptured viscus leading to peritonitis in the presence of a carcinoma of the cervix, and by the simple and common-sense method of making one diagnosis fit all the aspects of the case.

(*d*) As the patient was moribund on admission, treatment apart from that for the relief of pain was not attempted.

(*e*) An autopsy confirmed the diagnosis and the autopsy findings are reported.

Royal College of Obstetricians and Gynaecologists

The Quarterly Meeting of the Council was held in the College House on Saturday, October 25th, 1941, with the President, Professor W. Fletcher Shaw, in the Chair.

The Council approved changes in the Regulations for the Membership, to take effect in January, 1943.

The following were admitted to the Membership of the College:

Boyd, Gavin, Glasgow.
Gledhill, Edward, Batley.
Millen, Robinson MacIndoe, London.
Peaker, Constance Eileen, Leeds.
Robinson, Kathleen Marian, London.
Rogers, Katharine Churchill, London.
Sands, Richard Xerxes, London.
Sykes, Violet Evelyn Augusta, London.
Wynn-Williams, George, London.

Following the meeting the William Blair-Bell Memorial Lecture was given by Mr. W. C. W. Nixon, M.D., B.S., F.R.C.S. (Eng.), F.R.C.O.G., on "Diet in Pregnancy."

The following have satisfied the examiners for the Diploma of the College:

Barker, Elizabeth Georgina Wenmoth, London.
Beynon, Constance Lang, Brighton.
Cruttenden, Leslie Albert, Ripley.
Cunningham, Dorothy, Preston.
Denniss, Richard Greenwood, R.A.F.V.R.
Fyffe, Andrew Alexander, London.
Gammie, Robert Petrie, Bishop's Stortford.
Hallum, Jean Lilian, Birmingham.
Hefferman, Leslie William, Swansea.
Hollingsworth, Geoffrey, Macclesfield.
McNamara, Hilda Elizabeth, Canada.
Norris, Patrick Salmon, Pembury.
Thompson, Jean Freda, Leeds.
Watson, Harold Bernard, Birmingham.
Willett, Eva Marjorie Mawe, Southampton.
Wolskel, Harold Geoffrey, London.

BOOK REVIEWS

" Pictorial Midwifery." By Sir Comyns Berkeley, M.A., M.C., M.D., F.R.C.P., F.R.C.S., F.R.C.O.G. Published by Baillière, Tindall & Cox, 7 & 8 Henrietta Street, London, W.C.2. Price 7*s*. 6*d*.

That a 4th edition of " Pictorial Midwifery " is called for within 3 years of the last publication is evidence of the book's popularity. Some very useful additions to the text referring to certain of the pictures make the explanations clearer and more complete.

The section on the first stage of labour and mechanisms should prove particularly helpful as most pupils have difficulty in obtaining a sound grasp of these subjects. It is the experience of all midwifery teachers that, in class teaching, a clear representation is not possible without the aid of drawings, either in the form of diagrams or pictures. For the pupil who finds theory difficult and who is slow to understand and assimilate facts heard at lectures, the book will be invaluable.

The book is to be recommended for the use of teachers preparing for the Midwife-Teachers Certificate Examination. It should prove useful to them when planning a lecture, and the pictures, in modified form, as suggestions for their own blackboard diagrams.

In a library of current literature on midwifery, " Pictorial Midwifery " will be welcomed by both teachers and pupils.

E.A.C.-K., s.r.n., s.c.m.

" Handbook for Midwives." By Mary Mayes. Faber and Faber, Russell Square. Price 8*s*. 6*d*.

An excellent third edition, maintaining its original high standard. The chapter on Management of Breech is particularly to be mentioned; it is descriptive and concise, giving also a full summary of the dangers to both mother and child. This, together with the additional diagrams, convey to the student the great importance of a correct technique and management of delivery of the breech.

The present-day pupil may have difficulties to contend with in her midwifery studies, but these should be offset by such a textbook as that which Miss Mayes has written. It is well produced and the price is reasonable.

M. W.

Review of Current Literature

Director: Frederick Roques, M.A., M.D., M.Chir. (Cantab.), F.R.C.S., F.R.C.O.G.

This Review contains the lists of contents and abstracts of the more important articles from the journals with which the "Journal of Obstetrics and Gynaecology of the British Empire" exchanges.

The Review of Current Literature has kept the readers of the Journal in touch with current literature throughout the world; owing to the war many journals with which the *Journal of Obstetrics and Gynaecology* previously exchanged are no longer received. At the end of the year an Index of all the subjects contained in the articles of the journals reviewed is printed. Arrangements are also made to include abstracts of important articles on border-line subjects, such as Physiology, Biology, and Biochemistry.

LIST OF ABSTRACTORS

J. Lyle Cameron, F.R.C.S.; W. E. Crowther, M.B.; R. H. B. Adamson, M.D.; B. Jeaffreson, F.R.C.S.; P. Malpas, F.R.C.S.; T. N. A. Jeffcoate, F.R.C.S.; Meave Kenny, F.R.C.S.; Jane H. Filshill.

The Suture of the Perineum under Local Anaesthesia.

Professor F. J. Browne has drawn our attention to Dr. Neal Smith's paper on the above subject. Professor Browne states:

"I have read with much interest the article by Dr. Denys J. Neal Smith in the *Journal* of October, 1941, in which he describes and advocates the suture of perineal tears under local anaesthesia obtained by injection of 2 per cent novocaine and cites 17 cases so treated with satisfactory results.

"Thirteen years ago* I described an exactly similar method even to the insertion of the needle through the loin surface and stressing, as Dr. Smith does, the importance of infiltrating the tissues immediately under the skin or mucous membrane so that a weal is formed, the skin overlying the needle becoming slightly oedematous. The only difference between Dr. Smith's method and mine, so far as I can see, is that I advised the addition of adrenalin chloride solution (1 drop of a 1 in 1000 solution to each dram of novocaine) and pointed out that it spared the patient any pain from insertion

* "The Immediate Repair of the Torn Perineum under Local Anaesthesia," *Lancet*, 1928, i, 1281.

of the needle if a swab soaked in the solution was placed for five minutes beforehand against the raw surface.

"The method as described by me has been in routine use by the students and staff in the Obstetric Unit, University College Hospital for fully 13 years, both in the hospital and on the district; during that time it must have been used in several thousands of cases. The results have been so uniformly satisfactory that no one has suggested that it should be discontinued. To my knowledge the method is now routinely used in at least three other London hospitals."

British Medical Journal

April 19th, 1941.

Toxicity of stilboestrol. Editorial.

May 3rd, 1941.

Reactions after transfusion of stored blood. E. C. O. Jewesbury.
Dangers of posterior pituitary extract. Editorial.

May 31st, 1941.

*Intravenous anaesthesia in obstetrics. K. M. Robertson.

June 7th, 1941.

The calculation and prescribing of infants' feeds. (1) After the neonatal period. Helen M. Mackay.

June 14th, 1941.

*The calculation and prescribing of infants' feeds. (2) Neonatal period. Helen M. Mackay.

June 21st, 1941.

*Acute intestinal obstruction caused by twisted ovarian cyst. S. J. Navin.

July 5th, 1941.

Is the safe period safe? Editorial.

July 12th, 1941.

Treatment of impotence. A coitus training apparatus. J. Loewenstein.
*A case of double tubal gestation. A. E. Chisholm and Abigail Lesslie.
Lastation. Editorial.

July 26th, 1941.

Venous thrombosis and pulmonary embolism. Editorial.

August 26th, 1941.

*Massive adrenal carcinoma with pseudo-hermaphroditism. M. Albert.

INTRAVENOUS ANAESTHESIA IN OBSTETRICS.

Intravenous anaesthesia was tried because of the difficulty of working single-handed in domiciliary midwifery. Evipan was chosen for trial and was first used for perineal repair and later for low forceps delivery and other procedures. In 50 cases, reinforcement with ether was required once only. Ten c.c. was the usual dose employed, but a smaller dose was used in 7 cases to promote anaesthesia during spontaneous delivery of the head.

After the induction of anaesthesia, the forceps was applied with the patient in the lateral position. Better anaesthesia was obtained if the patient had received chloral, bromide or morphia earlier in labour.

THE CALCULATION AND PRESCRIBING OF INFANTS' FEEDS.

The baby should be put to the breast about six hours after birth. Three-hourly feeds, using both breasts at each feed, suit most babies, but at the end of a month five feeds a day, at four-hourly intervals, should be the rule. Lethargy and poor sucking is caused by a subnormal temperature, under-feeding, intracranial injury and other pathological conditions of the new-born.

After the first six days of life, a baby requires 50 calories per pound of body weight in 24 hours. The estimated calorie value of breast milk is 20 per ounce. Colostrum has a similar average calorie value, although there are wide variations. Therefore, in artificial feeding, dilute foods of low calorie value should not be used even in the first few days of life. Sweetened condensed milk (1 in 5) is advised for weak and premature babies and half cream dried milk with sugar for fully developed healthy babies. These foods provide 20 calories per ounce.

In calculating the amount of food to be given during the first week, the 50 calories per pound of body weight in 24 hours is used as the standard. One seventh of this amount is given on the first day and the total intake is increased by one seventh each day until the full calorie requirement is satisfied by the seventh day and thereafter maintained.

The same formula is applicable to premature infants although the total intake should be made up of a larger number of smaller feeds. Babies require fluid in addition to their regular feeds, an average requirement being 3 or 4 ounces of water daily from the second to fifth day of life.

Vitamin D should be given to all artificially fed children except those exposed to sunlight each day. Vitamin C is added to the diet later. Iron is advised for all children—even those breast-fed—between the second and twelfth months of life.

This article is illustrated by charts from which the food requirements of any baby can be easily ascertained.

ACUTE INTESTINAL OBSTRUCTION CAUSED BY TWISTED OVARIAN CYST.

An African woman, who had 7 children, was admitted complaining of constipation for 6 days and vomiting for 4 days. The pulse-rate was 160 and the abdomen was distended. A provisional diagnosis of volvulus was

made but laparotomy revealed a plum coloured ovarian cyst with torsion of the pedicle and the tube of the same side. The cyst was removed and spontaneous bowel action took place the day after operation.

The patient made a good recovery. The cyst was a dermoid and it is suggested that the intestinal obstruction was due to reflex nervous paralysis of the lower gut.

A Case of Double Tubal Gestation.

A woman aged 30, with 4 children, complained of continuous uterine haemorrhage for 5 to 6 weeks. She had had epimenorrhoea for 6 months. Examination under anaesthesia revealed bilateral swellings of the appendages. Curettage was carried out but no decidual reaction was found on microscopic examination.

At laparotomy nine days later, bilateral tubal pregnancies were found, the right Fallopian tube being the larger and containing a foetus. The left tube contained a mole.

Massive Adrenal Carcinoma with Pseudo-hermaphroditism.

A female child aged 2 years 2 months was admitted to hospital with a history of being fretful. Its mother had noticed a swelling of its abdomen for a few weeks. The child was wasted and had an enormous ovoid smooth mass in the right side of the abdomen. Hair was present on the pubis and in the axillae: the clitoris was enlarged.

At laparotomy it was found impossible to remove the tumour of the right suprarenal and the child died the following day. Post-mortem examination revealed it to be a carcinoma of the suprarenal cortex adherent to the diaphragm and inferior vena cava, with metastases in adjacent lymphatic glands.

Attention is drawn to the similarity between testosterone and corticosterone, and also the potential bisexual properties of the sex hormones.

T. N. A. Jeffcoate.

The Canadian Medical Association Journal

Vol. xlv, No. 1, July 1941.

*Congenital absence of the vagina. Melville C. Watson, M.B.

Congenital Absence of the Vagina.

Congenital absence of the vagina is due to the incomplete development of that part of the Müllerian system which enters into the formation of the vagina. Frequently it is associated with marked underdevelopment of the uterus, atresia of the cervix or absence of the Fallopian tube. Usually, how-

ever, the ovaries are present and functional to some degree. Seldom is the condition discovered before puberty, when absence of menstruation leads to investigation. Normal development of the body in general, and of the external genitalia in particular, is the usual rule. Usually the labia, clitoris, urethral meatus and even a hymeneal ring are well formed and there is a vaginal dimple.

The author cites three cases, in which absence of the vagina was not discovered till after marriage. Two of these cases did not experience any difficulty, the urethral canal being in each case dilated for a considerable part of its length, and this, together with stretching of the vaginal dimple, formed a kind of cloaca, which made coitus easily possible. These patients, although aware of amenorrhoea, were only concerned with the fact that they were sterile. The third patient experienced difficulties with coitus.

Two other cases which came for advice because of amenorrhoea are also mentioned.

Operative measures to establish a vaginal canal by transplanting epithelial tissues from skin, bowel, or foetal membranes, are associated with suffering, risk to life, inconvenience, and the possibility of failure in securing a desirable result.

Another method of treatment, by the application of well-directed pressure by means of dilators or obturators, has recently been described by Frank and has since been reported to be successfully employed by Holmes and Williams. This method, together with the encouragement of a proper mental attitude towards the condition, may be regarded as a mere pastime compared with the aforementioned operative methods. This latter type of treatment proved wholly satisfactory in the case of a girl of 15, who was otherwise well developed, but sought advice because of amenorrhoea. She was advised to leave matters till she was older, when she would understand the whole matter better. At the age of 18, her condition was fully explained to her and she was instructed in the use of instruments for the gradual elongation of the vaginal dimple in order that a new vagina might be obtained. The plunger from a small vaginal speculum was first chosen because of its length, size, and the shape of its handle, which was such as to make it easily controlled. With this instrument, intermittent pressure was applied to the area inside the vagina and directed upwards and backwards to avoid traction on the urethral meatus. This pressure was maintained for ten minutes each day for eight weeks, at which time a special bakelite obturator 2.5 cm. in diameter and 6.5 cm. in length was prepared and substituted for the original plunger. A special harness was at first employed to keep the plunger in place during the night. This was later discarded, as it was found unnecessary to wear it continuously. After a further period of eight weeks this obturator was completely accommodated by the newly formed vagina. After this, another obturator, of 9.5 cm. in length, was substituted.

The results obtained were entirely satisfactory. There was never at any time any discharge, no discomfort was experienced when inserting the obturator, the vaginal lining was not incised or broken and consequently there were no cicatrices requiring forcible stretching subsequently.

The author considers that this method of treatment is very satisfactory and that it should always be employed before resort is made to any operative procedure.

The author has appended a short bibliography, and an illustration is given of the plunger and two obturators.

J. LYLE CAMERON.

The Journal of the American Medical Association

Vol. cxvi, No. 4, January 25th, 1941.

*Treatment of uterine fibromyomata. W. Costolow.

*Iso-immunization in pregnancy and its bearing on erythroblastosis foetalis. P. Levine, E. Katzin, and L. Burnham.

Vol. cxvi, No. 7, February 15th, 1941.

*The gross effect on the small intestine of protracted deep pelvic irradiation. W. S. Wallace.

*Corpus luteum hormone. Dysmenorrhoea, after-pains, menstrual disturbances. G. W. Corner.

Vol. cxvi, No. 10, March 8th, 1941.

*Ovarian tumours of endocrine nature. E. Novak.

Vol. cxvi, No. 12, March 22nd, 1941.

*Renal insufficiency following transfusion. W. Daniels, B. Leonard, and S. Holtzman.

Vol. cxvi, No. 14, April 5th, 1941.

*Intertrigo treated with tannic acid and brilliant green. L. Tulepan.

*Ante-partum use of vitamin K in prothrombin deficiency in the newborn. G. Bohlender, W. Rosenbaum, and E. Sage.

Vol. cxvi, No. 22, May 31st, 1941.

*Post-menopausal osteoporosis. F. Albright, P. Smith, and A. Richardson.

TREATMENT OF UTERINE FIBROMYOMATA.

The cases described by the author were selected by other surgeons for radiotherapy. The analysis covers 986 cases treated by radiation, by X-rays, 33 per cent; by radium and X-rays, 61.5 per cent, and by radium alone 5.5 per cent. The advantage of combining X-rays with radium is that only small doses of each are necessary. The radium dosage usually used was 1,000 to 1,200 milligram-hours with a filtration of 1 mm. of platinum. The X-ray dose averages 450 r. units in the mid-pelvis.

No undue incidence of menopausal symptoms was observed, and the author considers that the radiation menopause does not differ from the normal menopause. With small tumours the uterus shrank to a normal size in 84 per cent of the cases, with tumours larger than a 4 months' pregnancy only 36 per cent of the uteri shrank to normal, but in all except 4 per cent there was some diminution in the size of the tumours. Subsequent operation was necessary in respect of this 4 per cent. Four, of the total of 986 patients, later developed uterine cancer; cancer of the body in 3 cases, 3 months, 1 year, and 5 years respectively after treatment; cancer of the cervix in 1 case, 6 years after treatment. This number is well within the normal limits of cancer incidence in an age group comparable to the series.

The age of the patient is the most important factor in deciding whether radiation should be preferred to surgery. The dangers of stirring up a quiescent pelvic infection have been overrated. In only one case was there any acute inflammatory reaction and this was in a case in which a curettage was done preceding the intra-uterine insertion of radium. Two large fibroids underwent acute necrobiosis and were removed successfully.

ISO-IMMUNIZATION IN PREGNANCY AND ITS BEARING ON ERYTHROBLASTOSIS FOETALIS.

This paper is an analysis of a number of cases in which atypical agglutinins in the blood were found associated with obstetric histories characterized by a number of complications such as toxaemia, abortion, intra-uterine death and neonatal death. In many of the cases it could be established that the infants suffered from erythroblastosis foetalis.

One typical case was that of a woman (Group O) who had 3 pregnancies, the first and third ending in neonatal death with post-mortem evidence of erythroblastosis. The second pregnancy ended in intra-uterine death at 8 months. The mother came to the notice of the authors because of anuria following a transfusion of her husband's blood, which was also in Group O. Atypical agglutinins could not be demonstrated on the day after the transfusion, only appearing some days later. This was to be expected since the donor's blood, still present in the patient's circulation, had specifically absorbed the atypical agglutinin.

Another case was that of a woman (Group A) with 2 spontaneous abortions, and 1 living full-time child. The fourth child, which died during labour, had hydrops foetalis. It was delivered by Caesarean section. The patient was given a transfusion from her husband, who was also of Group A, immediately after the operation. Four days later atypical agglutinins could be demonstrated acting on numerous bloods of Groups O and A. This patient died of transfusion anuria on the ninth day.

These transfusion accidents with apparently compatible bloods may be attributable to an agglutinin resulting from the immunization of the

mother by factors in the foetus inherited from the father. The connection which such cases seem to demonstrate between atypical agglutinins leading to transfusion accidents, and erythroblastosis foetalis, may explain both the aetiology of the latter condition and also its tendency to recur in successive pregnancies. The blood picture of the foetûs, with the destruction of red cells and a compensatory bone marrow reaction, may be explained by the iso-immunization theory. One may assume that atypical agglutinins in the mother's circulation penetrate the placental barrier and act on the foetal blood-corpuscles. In the presence of a sufficient concentration the foetus may die *in utero*.

There is evidence that most of these atypical agglutinins are parallel to the anti-Rh agglutinin of Landsteiner and Wiener. Rh is an antigen present in the red-blood cells of *macacus rhesus* monkeys and in about 85 per cent of human beings.

Obviously blood grouping tests should be done with great care when potent anti-A and anti-B sera are to be used, and particularly in cases of recurrent abortion or stillbirth, or erythroblastosis foetalis. It is safer to look for compatible donors among the patient's blood relatives than to use the husband's blood.

In an addendum to the paper the authors record 3 further cases when anti-Rh agglutinins were found in the mothers of infants suffering from erythroblastosis foetalis. In a further 3 cases however an Rh factor was present in the mother's blood, indicating that other blood factors may be involved or that an alternative explanation of the aetiology of erythroblastosis foetalis exists. The concept of an antigen-antibody reaction as a basis for the aetiology was first mentioned by Ottenberg and Darrow (*Journ. Amer. Med. Assoc.*, 1923, lxxxi, 295).

The Gross Effect on the Small Intestine of Protracted Deep Pelvic Irradiation.

This is a report of a radiological study of a series of cases of carcinoma cervicis receiving massive deep X-ray therapy. Certain characteristic post-irradiation changes were noted. The duodenum and jejunum were not grossly altered but the ileum showed characteristic changes, including segmentation of the barium stream, flattening of the mucosal pattern, diminished motility and narrowing of the lumen. Though these findings resemble those present in deficiency diseases, such as sprue, there is no direct evidence that the syndrome of X-ray sickness and diarrhoea bears any relation to the deficiency states.

Corpus Luteum Hormone.

Like all the articles in this series this review of the present state of our knowledge of the corpus luteum is so thorough that abstraction is almost impossible. Montaigne said " an abridgement of a good work is

a foolish abridgement," and this remark would be true of most of the articles in the series.

There is good evidence (Reynolds, 1939) that an inhibitory effect of progesterone on the uterus does occur in the human species. Since progesterone was isolated as a pure crystalline substance in 1934 it has been shown it can exist in two different crystalline forms and can be produced synthetically from a vegetable sterol known as stigmasterol. Though progesterone cannot be given by mouth a closely related substance, pregneninoline, is effective given orally.

Pregnandiol, isolated by Venning and Browne in 1936, is the excretion product of progesterone.

Corpus luteum therapy finds its main scope in the treatment of sequential and threatened abortion. Large doses are necessary (not less than 1 I.U. daily, and if possible 5 and even 10 I.U.s). Clinical results from smaller doses have been reported, but in the present state of knowledge 1 mgm. a day appears to be the least quantity that can conceivably have any effect. There have been no reports of any harmful effects in animals or women, even with large doses.

Dysmenorrhoea. A few reliable reports have been published of improvement in primary dysmenorrhoea with the use of progesterone, say 2 I.U.s for 3 or 4 days before the onset of the period.

After-pains. These have been reported to have been relieved by the drug.

Menstrual disturbances. Despite favourable reports the value of progesterone therapy in both menorrhagia and amenorrhoea still remains obscure. No corpus luteum products other than assayed progesterone preparations should be used and they no doubt will become obsolete now that genuine assayed products are available.

Ovarian Tumours of Endocrine Nature.

The ovarian tumours with an established endocrine activity are (1) granulosa-cell carcinoma, (2) thecoma, (3) luteoma, (4) arrhenoblastoma, (5) adrenal ovarian tumours, (6) the so-called struma ovarii or thyroid tumour of the ovary. All, with the exception of the last two, are due to abnormalities in the early stages of gonadogenesis. Novak proceeds to summarize the stages in the development of the ovary. He considers Meyer's explanation is the best working explanation of the histogenesis of these tumours, particularly with regard to the persistence of male-directed cells in the ovarian medulla, from which the arrhenoblastoma develops. The rest of the paper is concerned with the established clinical symptoms of these tumours, particularly the granulosa-cell tumours and the arrhenoblastomas.

Renal Insufficiency Following Transfusion.

The authors describe 13 cases of renal insufficiency following blood-transfusion. Seven of the patients died. In 6 of the cases in which the blood grouping or cross matching was checked the blood was found incompatible in 4. They recommend more careful cross matching of the bloods by the use of tube preparations incubated at 37.5°C. for one hour, and also the administration of alkalis to all patients before transfusion.

Intertrigo Treated with Tannic Acid and Brilliant Green.

The affected parts are sprayed with a 5 per cent solution of tannic acid. If a secondary infection is present a 2 per cent solution of brilliant green is sprayed over the tannic acid layer. Before application of the sprays the parts are washed with soap and water and thoroughly dried.

Ante-partum use of Vitamin K in Prothrombin Deficiency in the Newborn.

Soon after birth the prothrombin level of the infant's blood falls to a very low level. Workers are not quite agreed whether the blood has a low prothrombin content at birth or whether the fall occurs soon after. Shettles, Delfs and Hellmann (*Bull. Johns Hopkins Hosp.*, 1939, lxv, 419) concluded that the plasma prothrombin level can be raised, not only by giving vitamin K to the infant, but also to the mother before delivery.

The present report deals with 50 infants whose mothers were given vitamin K before delivery, with a control group of 50 untreated patients. The product used was 4-amino-2 methyl-1 naphthol hydrochloride, a synthetic preparation having vitamin K activity, 1 mgm. per cubic centimetre. The clinical test the authors used was one devised by Quirk and others, measuring the clotting time of oxalated plasma when the plasma is mixed with an excess of thromboplasten and an excess of calcium. By this test a high prothrombin time denotes a low prothrombin concentration. The conclusions of the authors were as follows:

1. The prothrombin time shows a big rise during the first week of life.

2. A vitamin K preparation effectively prevents prothrombin deficiency in the newborn.

3. The time of administration of the vitamin K to the mother does not appear to make any difference in the results obtained.

4. The infant's cord prothrombin time averages more than 2 seconds more than the mother's prothrombin time.

5. The preparation used has no toxic effects on the infant.

6. The preparation used readily passes through the placenta.

7. The vitamin should be given routinely as a prophylactic measure when the infant is likely to be premature, labour is prolonged or operative delivery of any type is anticipated.

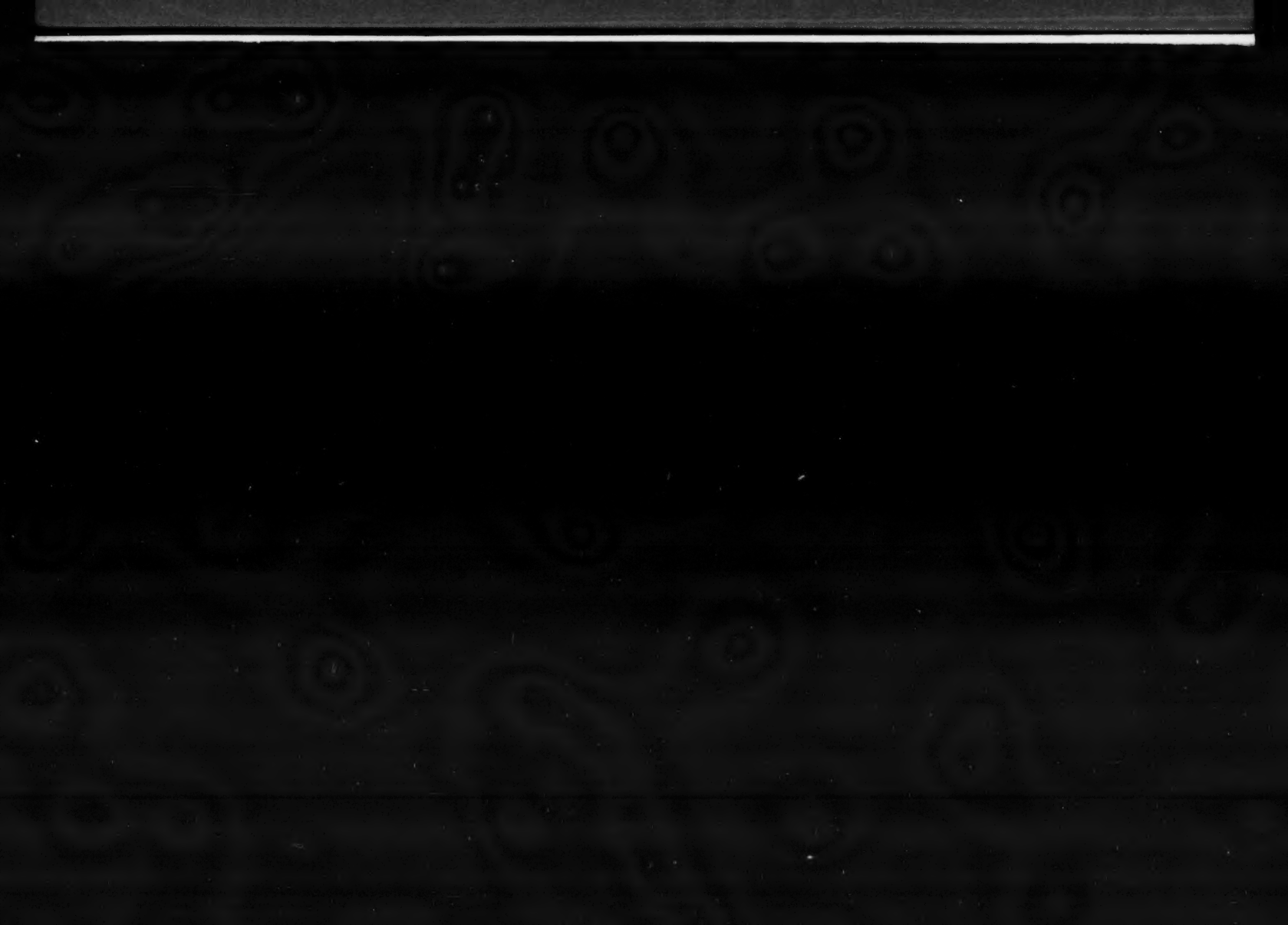
(This is an important paper, but would be more valuable still if all

the data had been given. The average cord prothrombin time in the control group was 17.42 seconds, in the treated group 18.22 seconds, figures rather at variance with the main contention of the paper.)

POST-MENOPAUSAL OSTEOPOROSIS.

The authors believe that osteoporosis is not a disorder of calcium metabolism but rather an atrophy of the bone matrix. The main factors in the causation of osteoporosis are disuse and senescence; faulty diet is not a factor. Because the condition constantly occurs after the menopause, and oestrin therapy has a beneficial effect, the authors conclude that the post-menopausal state is the most important basic aetiological condition. They only found 2 cases in men, and none in women prior to the menopause. Three of the 42 patients had had thyrotoxicosis. There is evidence that patients with post-menopausal osteoporosis have a tendency to atrophy of other tissues, notably the skin. It is interesting to note that 10 of the 42 patients were women who had had an artificial menopause induced. There was no statistically significant difference in the time of onset of symptoms after the artificial menopause as compared with the normal menopause. The time varied between 9 years and 13 years.

PERCY MALPAS.



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